Brain

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BRAIN.

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THE HISTOLOGY OF CEREBRAL ŒDEMA ASSOCIATED WITH INTRACRANIAL TUMOURS (WITH SPECIAL REFERENCE TO CHANGES IN THE NERVE FIBRES OF THE CENTRUM OVALE).

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LOCAL œdema of the brain has long been recognized to occur round tumours and abscesses. More general swelling of the brain has been found also in cases of catatonia and epilepsy and has been thought to account for many of the symptoms of cerebral injury and uræmia. In spite of this there is much diversity of opinion as to the histological changes which accompany swelling of the brain and indeed, from what has been written, it would appear that different causes produce such different histological appearances that only confusion can result from any attempt to group them together.

General swelling of the brain has also been said to occur as an autolytic phenomenon so that if the post-mortem examination is delayed for more than twenty-four hours the convolutions may appear flattened and the sulci less patent than normal. Swelling of the brain tissue must also be clearly distinguished from the so-called œdema of the meninges which may be said to be the reverse of cerebral œdema since it results from shrinkage of the brain with the attendant widening of the subarachnoid space.

The normal correlation between brain volume and skull capacity was established by Rieger (1885), and Reichardt (1905), using his method, laid it down that the brain may be considered swollen when the difference between these measurements was less than 8 per cent. He initiated the conception of "brain swelling" which he defined as a definite increase in the volume of the brain, not due to hyperæmia or to excess of free fluid. This he found in katatonia, epilepsy, and various infections and intoxica-

tions. He considered it to be due to an alteration in the colloidal chemistry of the brain tissue which produced no definite histological changes. Wohlwill (1914) demonstrated the presence of Alzheimer's amœboid glial cells in many toxic and infectious diseases associated with brain swelling. Spatz (1929) distinguished "brain swelling" from œdema. In "brain swelling" there was a general increase in size of the whole hemisphere, with an increased consistency and a dry condition of the brain substance. In œdema the brain tissue was softer and wetter than normal. He described "symptomatic brain swelling" in cases of cerebral tumour which affected not only the whole of the hemisphere in which the tumour lay, but often also the opposite hemisphere. The medulla, as well as the uvula and tonsils of the cerebellum and the optic nerves, might be involved in the same process. He found little definite histological change in association with symptomatic brain swelling. In some cases there was swelling of the processes of the astrocytes in the white matter, often with dissolution of these processes (Clasmatodendrosis), and the amœboid change of Alzheimer which was more widespread than in any other condition. There were also slight swellings of the processes of the nerve cells in affected areas. Jaburek (1935), on the other hand, did not consider that any sharp distinction could be made in cases of cerebral tumour between brain swelling and œdema. He defined the histological changes of œdema as exudation of fluid with the formation of spaces and holes in the tissues, separation of the neuroglial meshwork, and of the perivascular and pericellular spaces. He found the greatest tendency to œdema in malignant tumours, such as carcinomas, fibro-sarcomas and many kinds of glio-sarcomas, whereas the better differentiated gliomas, as well as the endotheliomas and angiomas, did not produce it. He considered that it was a toxic or inflammatory process spreading out from the tumour. He made the interesting discovery that certain tissues of the brain had a special tendency to œdema, whereas others were rarely affected. The white matter of the hemispheres was particularly liable, but the large commissural nerve tracts, such as the internal and external capsules, the corpus callosum and the anterior and posterior commissures were not affected. Other areas which were not affected were the grey matter of the cortex and basal ganglia, and the whole brain stem (including the cerebellum and the diencephalon). Scheinker (1938) also described œdema in cases of cerebral tumour. The histological changes found by him included increase of neuroglial nuclei, many of which were degenerated and their cell body disintegrating, congestion of vessels, widening of the perivascular spaces and general loosening of the ground substance, without any forma-

tion of neuroglial fibres or fat granule cells. He noted also irregular swelling of the myelin sheaths and axis cylinders and of the bodies of the neuroglial cells. In some places there were localized areas of softening of the tissues. In the cortex he found widening of the pericellular spaces, and acute cell disease of the neurones in the most affected areas. He also could find no sharp distinction between brain swelling and œdema; they were different grades in the same process of pathological hydration and swelling of the nervous parenchyma. While these authors laid special emphasis on the changes in the white matter, Le Beau (1938), on the basis of some experimental studies by del Rio Hortega, considered widespread swelling of the nerve cells of the cortex as the histological criterion of œdema in cases of cerebral tumour.

The histological changes in general swelling of the brain from other causes have been described by various authors. Struwe (1931) described the appearances in a number of cases of mental disease (catatonia, manic-depressive psychosis, epileptic dementia) in which death occurred suddenly from brain swelling. He found small localized areas in the white matter in which there was poverty or almost complete disappearance of myelin sheaths, those present being very thin or irregularly swollen. No products of lipoid katabolism were, however, seen. The axis cylinders in these areas were unaltered. Changes in the macroglia were more widespread and varied from clasmatodendrosis to complete destruction. The severest changes in it were seen in the cortex and the deeper layers of white matter, whereas it was relatively well preserved in the subcortical U fibres. In Sommer's sector of the Cornu Ammonis it was often completely destroyed. The Nissl picture of the cortex was, however, normal. Early progressive changes could be seen in the microglial cells and more pronounced changes in the oligodendroglia, the processes of which stained with unusual ease. In the cortex the oligodendroglial satellites might contain fine granules of iron. No vascular changes could be seen in these cases except congestion and occasional small hæmorrhages.

Terplan (1937) described the histological changes, associated with marked swelling of the brain, in two cases of insulin shock, three of acute encephalitis in children, one of which was associated with hypoglycæmia, one case of burns, one of poisoning by oleum chenopodium, and one of cerebellar cyst. In these cases there was swelling of the entire cortex with loss of its normal architecture. The nerve cells of the 3rd and 5th layers were almost entirely destroyed and those that remained showed colliquative or ischæmic necrosis. The endothelium of the capillaries was swollen. In one patient who lived for eleven days after the onset of unconsciousness

the nerve cells of the 3rd layer of the cortex were replaced by a dense network of proliferating capillaries. These changes were not seen in the basal ganglia which were relatively normal.

It appears, therefore, that what is described as brain swelling in cases of insanity and various infections or intoxications may be a totally different histological process from the œdema related to brain tumours, on which, except for the assumptions of Le Beau, there seems to be a measure of agreement.

These histological studies have been supplemented by investigations of the relationship between the wet and dry weight of the brain tissues. Alexander and Looney (1938) found by this method that œdema was almost entirely confined to the white matter of the brain since the grey matter of œdematous brains kept the normal ratio between wet and dry weight. Both they and Schlüter and Never (1932) found, however, that it was impossible to judge the presence or the degree of œdema from a comparison of wet and dry weight since a relative increase of water was also found in atrophied and in hydrocephalic brains.

The difficulty of assessing the degree or even the presence of œdema in fixed brains makes it important to have some histological criteria. In cases of cerebral tumour the œdematous area is usually confined to the side of the tumour. As Jaburek has shown it does not affect the corpus callosum and is, therefore, unlikely to spread to the opposite hemisphere. It is, therefore, possible in these cases to compare the œdematous area with normal white matter from the same brain and thus avoid any fallacies arising from the mode of death or from post-mortem autolysis. It was also hoped that the study of the histology of œdema in relation to cerebral tumours might throw some light on its pathogenesis. It is recognized, however, that the process in cases of cerebral tumours may be quite different from that in general disease and intoxications, and no deductions as to the histology of general œdema or swelling of the brain should be drawn from the present study.

The macroscopic appearances of œdema in relation to cerebral tumours or abscesses are well known and in severe cases one can be certain of its presence. In such cases the white matter appears yellowish and soft, and when it lies on the slab fluid pours from it in considerable quantity. The degree of discolouration is variable and appears to depend to a considerable degree on the cause since it is usually greater in cases of cerebral abscess than in those of tumours. The discolouration gradually fades off as one passes away from the tumour or abscess to which the œdema is related, but it may be very extensive. In less severe cases there is no alteration in

colour and the presence of œdema can only be judged from an increase in the size of the centrum semi-ovale and its softer consistence as compared with the normal hemisphere. In addition the convolutions look wider than normal from the swelling of their white centres. By comparison with the swollen white matter the cortex may look shrunken. Actually, by measurement it is found to be little, if at all affected. Œdema does not appear to occur either in the basal ganglia or brain stem. If it does it fails to cause any macroscopic changes. It may, however, affect the white matter of the cerebellum and is commonly seen round abscesses in that situation. Œdema of the spinal cord also occurs but is not considered in the present study which is confined to the cerebral hemispheres.

Material and Methods.

The material studied came from 28 cases of cerebral tumour. For purposes of comparison two cases of cerebral abscess were studied. Fairly large blocks of tissue, sometimes comprising the whole coronal section of a hemisphere were embedded in celloidin and stained by a variety of methods. For technical reasons frozen and paraffin sections were found less suitable than celloidin sections, but for certain methods frozen sections of material embedded in gelatine were used. Methods which depend on special fixation, such as Alzheimer's fuchsin-light green method, were not used. The latter method was used by Alzheimer and Wohlwill in extensive studies of the neuroglial reaction in cerebral œdema and other conditions, but for the purposes of the present study it was considered less important to study the neuroglial reaction intensively than to compare in neighbouring sections the changes seen in the astrocytes with those in the neurones including the axon and myelin sheath.

An earlier study of cases of old-standing injury of the brain had suggested that the widespread demyelination seen in these cases might result to some extent at least from cerebral œdema and, therefore, in the earlier cases of cerebral tumour examined only the Weigert-Pal method was used. This showed that characteristic changes in the myelin sheaths of the centrum semi-ovale of greater or less degree were constantly found in cases showing a degree of cerebral œdema which could be recognized by the naked eye. However, the fact that the changes to some extent resembled those produced by autolysis made it necessary to examine other elements such as the axis cylinders and neuroglia in which autolytic changes are more readily distinguished from those occurring before death. In addition to the ordinary tissue stains such as hæmatoxylin with van Gieson and Nissl's method, Mallory's phosphotungstic acid hæmatoxylin

and in some cases Mallory's "connective tissue stain" (acid fuchsin-aniline blue-orange G.) were used for neuroglial cells and fibres, the Loyez method for myelin sheaths, and the Gros-Bielschowsky method for axis cylinders.[1] Lipoid degeneration was studied in sections from neighbouring blocks of tissue stained by Scharlach R and hæmatoxylin usually after gelatine embedding. The cases studied included five of metastatic malignant nodules in the brain, nine of endothelioma, one of hæmangioblastoma and thirteen of cerebral glioma.

Alterations in Nerve Fibres.

The most obvious change seen in cases of cerebral œdema studied by the Weigert-Pal method is a diffuse pallor of the centrum ovale. In most

Fig. 1.—Secondary nodule from bronchial carcinoma embedded in white matter of frontal cortex. (Weigert-Pal counterstained with alum carmine.) There is a zone of œdema with partial demyelination round the nodule; this spares the subcortical fibres in most places.

[1] The Gros-Bielschowsky method employed was the modification for celloidin sections devised by Dr. D. Denny-Brown (Carleton, Histological Technique 2nd Ed.) to whom the writer wishes to express his gratitude for help in interpreting the changes in the axis cylinders.

FIG. 2.

FIG. 3.

FIG. 2.—*Case 3.* Secondary nodule from renal carcinoma in subcortical white matter. The demyelination does not affect the myelinated fibres in the cortex (Loyez myelin stain).

FIG. 3.—*Case 3.* Coronal section through the frontal lobe and genu of the corpus callosum. There is widespread œdema and demyelination which, however, does not affect the corpus callosum. (Weigert-Pal.)

FIG. 4.

FIG. 5.

FIG. 4.—*Case 11.* Fronto-temporal glioma. Coronal section through right parieto-occipital region and splenium of corpus callosum. There is extensive œdema and demyelination which affects the optic radiations slightly and the corpus callosum not at all. (Weigert-Pal counterstained alum carmine.)

FIG. 5.—*Case 9.* Glioblastoma in relation to the posterior horn of the right lateral ventricle. Coronal section through right occipital lobe. The tumour (unstained) lies just internal to the ventricle. The optic radiations are stretched out by it but not demyelinated as much as the white matter external to them. The fibres going to the splenium of the corpus callosum, though they lie close to the tumour, are well stained. (Weigert-Pal counterstained carmine.)

cases this gradually recedes as one passes towards the cortex, but in severe cases it may be almost equally intense over the whole of the centrum semi-ovale, with the exception of the subcortical U fibres which are comparatively unaffected. In severe cases, and especially in those associated with cerebral abscess, these fibres also may remain comparatively unstained. There is a remarkable tendency for certain fibre systems to be spared either relatively or absolutely. For example the corpus callosum was never affected in the cases studied, and in cases involving the white matter of the occipital lobe the optic radiation was more deeply stained than the rest of the white matter (figs. 1-5). The possibility that pallor of the white matter might be entirely explained by a separation of the fibres by interstitial fluid is ruled out when the sections are examined under higher magnifications. It is then seen that very many of the fibres are beaded or irregularly swollen or show larger single swellings. These changes are as obvious in brains removed within an hour or two of death as in those in which a greater delay has occurred and are always more intense in the palely stained œdematous area than in those areas that stain more darkly. In severe cases the demyelination is much greater, and only sparse irregularly swollen myelin sheaths may be seen in the most affected areas, much of the lipoid appearing as fine granules or larger globules which stain with hæmatoxylin. But the margin is always indefinite, even when the transition from pale centrum semi-ovale to darker sub-cortical U fibres appears to the naked eye to be fairly abrupt (figs. 6-9).

In sections stained by Scharlach R it is unusual to find more than the earliest stages of myelin katabolism. A few phagocytic cells, especially near the vessels, contain granules which stain more orange than normal myelin, but very few granules which take the full red stain of fats or fatty acids can be seen. These early stages of myelin katabolism can be compared with the much greater degree of lipoid change which is sometimes seen in the softened zone immediately round the tumour. In the cases of cerebral abscess the katabolism of myelin had progressed much further, with the presence of many fat granule cells, but this was unusual in the œdema related to a cerebral tumour. Sometimes phagocytic cells (myeloclasts) could be seen inside the globular swellings of the myelin sheath, an appearance described by Jakob in secondary degenerations in the spinal cord (figs. 14 and 15).

The *changes in the axones* were studied in celloidin sections stained by the Gros-Bielschowsky method. They were less obvious than those in the myelin, and were in all cases of less severe degree, although in some severe cases, in which the œdema appeared to have been present for some days,

considerable rarefaction of axis cylinders was found. In some cases in which the œdema appeared to be recent the axones were varicose, often with a ragged outline, and end bulbs were difficult to find, or were only seen on the fine fibres. In other severe cases end-bulbs and cocoon-like swellings on the course of the larger axones, and irregular swellings of the finer fibres, were seen in every microscopic field. In milder cases end-bulbs and large cocoon-like formations were absent or difficult to find, but many small fusiform swellings on the course of the fibres were seen. The latter appearance did not differ greatly from what may be seen in post-mortem autolysis, but it was as common in brains which were removed very shortly after death as in those in which there had been more delay (figs. 10, 11 and 12).

Neuroglial Reaction.

In all cases of moderate or severe œdema, swelling of the cell bodies of the astrocytes could be seen. This varied from the appearance of a small tag of cytoplasm at one side of the nucleus, to the presence of large bodied astrocytes, some of which had more than one nucleus. In certain cases there also appeared to be an increase in the number of astrocytes and it was not uncommon to find two or more lying close to one another as though they had arisen from the division of a parent cell. In bi-nucleated cells the nuclei might lie at opposite poles of the cell body, which was sometimes no wider than the length of the nuclei. Sometimes, however, they lay close together. Not uncommonly the nuclei in swollen astrocytes were irregularly enlarged, and might be elongated or reniform or even lobed like those of a polymorphonuclear leucocyte. In all except the most acute cases the enlarged astrocytes gave rise to fibres and in what appeared to be more chronic cases there was a definite or even great excess of neuroglial fibres throughout the œdematous area (figs. 18 and 21).

The appearance of the neuroglial cells in more acute cases were less easily analysed. Here the swollen cells were not all of one type as in the cases of less severity, but rather appeared to be divisible into four main groups. The first included cells with a large ill-defined irregularly shaped mass of cytoplasm, which appeared to fill up the interstices of the surrounding tissue rather than to push the fibres apart. It contained a nucleus which was sometimes of the size and shape of an astrocytic nucleus, but stained palely and diffusely (fig. 20). Sometimes these nuclei were so pale as to be invisible except with a high power objective. It was unusual to find reniform or elongated nuclei in this type of cell. Sometimes, however, the nucleus was shrunken and hyperchromic (pyknotic) but it never looked healthy.

The second type of cell, which might be seen in the same field as the first, but was much less abundant, consisted of a nucleus of normal astrocytic size but with scanty chromatin which was arranged as fine granules under the nuclear membrane, and a rather rounded cell body which was less swollen than in the first form, stained greyish with hæmatoxylin and sometimes appeared granular (fig. 16). A third type of cell had an irregularly shaped, sometimes swollen nucleus which often showed degenerative changes. The cytoplasm was swollen, irregularly rounded or oval and contained many fine granules (fig. 19). These three types were considered to be degenerating forms of astrocyte. None had any definite fibres attached to them, i.e. they had undergone clasmatodendrosis.

A fourth type of cell, which might be diffusely distributed, but was specially common near the walls of vessels, consisted of a small darkly staining nucleus which might be irregularly rounded, oval, reniform or elongated and a well-defined oval cell body full of fine granules, some of which stained purple with Mallory's phosphotungstic acid hæmatoxylin (fig. 17). This type of cell was thought to be derived from the microglia and to be an early form of lipoid phagocyte. The character of the nucleus and the tendency which these cells showed to collect near the walls of blood-vessels, suggested this derivation.

In cases in which these types of cell appeared there were often clear oval spaces in the tissues which usually did not contain any nucleus or cell. In only one case of cerebral tumour did they contain any stainable colloid and it appeared probable that they resulted from the shrinkage of the softened tissues during fixation and did not represent pre-existing spaces. It is important to note that in cases of this severity neuroglial fibres could not usually be demonstrated, though in one or two cases a few, rather thick, irregularly curved, neuroglial fibres could be seen, and occasionally smaller more granular fragments.

In each individual case the changes in the astrocytes tended to be of the same type and much the same degree, although their intensity decreased on passing toward the periphery of the affected area. They were found throughout the area in which the myelin stained palely but could no longer be found where the myelin was normal.

The *oligodendroglia* appeared to be little affected in the majority of cases studied. Only in acute and severe cases was there any evidence of swelling of the cell body and the changes then seen were scarcely more than those found in many cases in which the post-mortem examination has been delayed for twenty-four hours or more after death. The nuclei always

remained relatively normal, although they sometimes appeared to be rather shrunken and their chomatin more granular than normal.

Cerebral Cortex.

In the milder degrees of œdema related to tumours of the brain the cortex looked microscopically normal. There was no evidence of the generalized swelling of nerve cells which has been postulated by Le Beau as constituting the essential change of cerebral œdema. In only one case was there slight swelling of the neurones of the 5th layer, and this was interpreted as being an early axonal reaction due to the severe degeneration of their axones in the underlying white matter. In many of the severer cases ischæmic degeneration was seen in a certain number of the neurones. Its irregular incidence or patchy distribution indicated that it was not due to autolytic processes. It one case severer cell changes were present in some of the neurones of the 3rd layer. These cells were surrounded by fine granules due to degeneration and swelling of the boutons terminaux.

The slightness of the change in the cortex contrasted with those found in the cases of cerebral abscess and in one case of post-operative thrombosis of a superficial vein. In the former cases there was definite swelling of the bodies of the astrocytes and proliferation of the microglial cells as well as severe degeneration of many of the cortical neurones. These changes may be attributed to the direct effect of toxins emanating from the abscess. In the case of venous thrombosis most of the cortical neurones showed severe ischæmic changes; they were irregularly shrunken and many of them had receded from the surrounding tissues leaving a clear zone. In this case there was also some swelling of the cytoplasm of the astrocytes and increase in the numbers of microglial cells and oligodendroglial satellites. These changes resemble those seen in minor degrees of arterial obstruction and appear to result from anoxia of the tissues. Swelling of nerve cells was not seen either in this case or in others with extensive sinus thrombosis involving many of the large superficial cerebral veins.

Relations of type of tumour to severity and acuteness of the histological changes interpreted as "œdema."

It is generally recognized that severe œdema is more commonly associated with certain kinds of tumour than with others. Secondary carcinomas, for example, frequently appear to produce severe œdema round themselves, although at other times the masses of cancer are embedded in what appear to be healthy brain. It seemed, therefore, possible that an analysis of the relationship between the type of tumour

and the degree or acuteness of the process, which it is convenient to call œdema, might throw some light on its pathogenesis. Although a much larger series of cases would be needed to establish this relationship in any definite manner, certain indications may be drawn from the comparatively small numbers in this series.

It will be convenient for the purposes of this analysis to assume that some idea of the duration of the œdema can be gained from the degree and type of reaction of the astrocytes. For example, it is generally agreed that the formation of new neuroglial fibres is a process requiring a certain amount of time. Whether this should be reckoned in hours or days is, however, a matter of speculation. The type of swelling of the cell bodies of the astrocytes which is associated with healthy nuclei and preservation of fibres also seems to be a change which requires some little time, probably several days, to develop. And, therefore, in cases in which the cell bodies were greatly swollen and in which many bi-nucleated cells were seen, the œdema was assumed to have existed for several days before death. On the other hand in cases in which the neuroglial swelling was of the amœboid type, with the presence of granular cells of microglial origin, it was difficult if not impossible to gauge the duration of the œdema, although its severity was evident enough. The changes in the axis cylinders are not much assistance in assessing the length of time that œdema has been present since these may be very precocious. Rand and Courville (1934) in cases of head injury found swellings and end bulbs on the small fibres as early as two hours, and larger end bulbs four hours after the accident.

Applying these criteria to the changes seen in this series of brains it was found that the most acute and severe changes, with the presence of amœboid glial cells, occurred in two cases of secondary carcinoma (one bronchial, the other renal), and three cases of glioblastoma, one of which had seeded over the walls of the posterior horns of the ventricles. At the other end of the scale mild diffuse changes, with the presence of Nissl's "plump" astrocytes and overgrowth of neuroglial fibres, were found in three cases of endothelioma and in four of the more slowly growing forms of glioma as well as in one case of secondary nodules from a hypernephroma. The other cases studied either showed early changes of moderate intensity or were complicated by some factor such as recent operation which made them unsuited for purposes of comparison. So far as one can draw any deduction from this survey it appears that rapidly growing tumours, whatever their nature may be, are apt to produce the more acute and severe degrees of œdema, whereas the slowly growing tumours usually give rise to a subacute process.

Nature and pathogenesis of œdema in relation to cerebral tumours.

The histological changes in the swollen areas of brain near brain tumours have been seen to include (1) Pallor of the myelin staining, due partly to separation of the fibres, and partly to changes in the myelin which may result in katabolism of much of it into granules and globules of material which still stains by hæmatoxylin. (2) Varicosities, irregular swellings, and the formation of end bulbs on the axones. (3) Swelling either of an acute and destructive (regressive) or a subacute and formative (progressive) character in the astrocytes. (4) Slight mobilization of the microglia with early lipoid phagocytosis.

Various questions as to the nature and pathogenesis of these changes arise. First, if not in importance at least in historical sequence, comes the old question whether the process should be called brain swelling or cerebral œdema. These terms have been applied to the macroscopical rather than the microscopical appearances: that of brain swelling to a condition in which the brain or a part of the brain is swollen, firmer than normal and dry, and œdema to a condition in which the brain is swollen, softer than normal and exudes fluid on standing. These criteria can only be applied to the brain in its fresh state, and it has been stated by Le Beau that areas which when fresh appear soft and wet may become, after fixation, firmer than the normal brain tissue. In the present series this was rarely found ; the areas which were soft when fresh never fixed firmly, and it was difficult, if not impossible, to obtain frozen sections from them without gelatine embedding. Pötzl and Schüller (1910), Jaburek (1936) and Scheinker (1938) in histological examinations of brain swelling and cerebral œdema found a gradual transition between the appearances in the two forms. This opinion is confirmed by the present study which indicates that the term œdema has been applied to the more acute and severe stages of a process which if less acute produces what has been called brain swelling.

It seems, therefore, best to use one name only for this process and the term œdema has been chosen. This name indicates that the swelling is due to fluid in the interstices of the tissue, but does not exclude the possibility of secondary changes in the cells and fibres. In the present series of cases it was found that myelinated fibres in œdematous areas were less closely packed together than in the normal brain, but histological evidence of interstitial fluid could only be found in one case. It appeared, therefore, probable that the substance between the fibres was not stainable by the methods employed. But that the fibres were separated by fluid there seems little doubt. The nature of this fluid cannot be determined by histological

methods but it probably differs little from the normal interstitial fluid of brain tissue.

Of the histological changes which have been seen to occur in areas of œdema, the only one which is directly attributable to an increase of interstitial fluid is, therefore, the pallor in sections stained for myelin, due to separation of the fibres. The other changes are merely accompaniments of œdema and although constantly present in the present series, they may not always be associated with it. The question, therefore, arises whether they are independent or in some way dependent on the excess of interstitial fluid. That they are not related directly to the pressure exerted by the tumour is shown by the fact that they are rarely present in equal degree all round it; in fact the tissues may be normal histologically to within 1 cm. of the tumour on one side although the changes associated with œdema may spread for 5 cm. or more away from it in another direction.

The changes in the neuroglial cells and myelinated fibres are similar to those which are commonly found in cerebral anoxia, and anoxia in the neighbourhood of cerebral tumours might result either (1) from pressure on veins or involvement of veins in the tumour; (2) from capillary compression; or (3) from the stasis of interstitial fluid in the brain tissues. If the changes were due to anoxia their absence from tissues, such as the grey matter, which have a richer blood supply, could be readily explained.[1] Which of the three factors suggested is chiefly responsible for them in individual cases it is impossible to state on the evidence so far available. In cerebral tumours of all kinds there must come a time when the general intracranial pressure tends to compress the veins. This pressure is probably not evenly distributed within the cranial cavity owing to the firm dural septa and its greatest effects may be quite local. It was found, however, that dilatation of capillaries and small vessels was not a necessary accompaniment of œdema. It was found in this series only in the cases of endothelioma. If the abnormal transudation of fluid into the tissues were due primarily to this pressure on the veins, its anoxic effects would be increased by the compression of the capillaries, and a vicious circle would be established whereby the more the veins were compressed the more fluid would be transuded and the less room there would be for capillary blood. The simplest explanation for the association of the changes of anoxia with those of œdema is, however, the third suggested, i.e. that the stasis of

[1] On the other hand, it has been seen that ischaemic changes are often present in the cortical neurones.

excessive interstitial fluid in the issues prevents them from receiving their normal supply of oxygen from the capillaries.

The changes accompanying œdema in relation to cerebral tumours shed no light on its causation. The most probable causes are either pressure on veins, or the effects of toxins or metabolites from the injured brain tissue or from degeneration of the tumour itself. The possibility that tumours may involve more or less directly the veins which drain the œdematous area has already been mentioned. Metabolites from the damaged brain tissue or from degenerating tumour substance may cause œdema either by altering the osmotic relationship on the two sides of the vessel walls or by directly poisoning the walls of the capillaries. Of the latter process the histological studies in this series have given no evidence. While there may be severe destruction of myelinated fibres in the immediate neighbourhood of a tumour, the fact that the area of œdema is not necessarily concentric with the tumour is against the assumption that œdema is due to metabolites passing out from the tumour unless tissue fluids pass more freely in certain directions than in others. It can, however, be said that in some cases in which cancer nodules were embedded in the centre of the white matter of a hemisphere, the area of demyelination round them was almost concentric with the margin of the tumour.

Illustrative Cases.

Secondary Carcinoma.

Case 1.—C. R., aged 52. (Case No. 51/1937.) *Secondary nodules in brain from a bronchial carcinoma* (*Columnar celled carcinoma forming acini and alveoli*). Post-mortem examination twenty-four hours after death.

On removing the brain a superficial softened area in the right angular gyrus fell out, releasing rather thick mucopurulent material. In front and behind this area the right hemisphere was very soft and swollen. No other deposits of growth were found in the brain.

Histologically there was no increase of nuclei in the softened area of brain, and no evidence of inflammation except a single layer of lymphocytes in the perivascular space of one of the subcortical vessels. The cell bodies of all the astrocytes were swollen, some forming a rounded body about twice the diameter of the nucleus with sharply defined margins, others an irregularly defined mass of considerably larger size. In some of the latter the nucleus stained faintly and diffusely grey; in others the nucleus was considerably larger than normal and was paler and more vesicular than normal, its chromatin was arranged in coarse granules under the nuclear membrane and there was usually a well-stained nucleolus. Other smaller cells, in which the cytoplasm stained faintly grey with hæmatoxylin, had a pale nucleus of normal size in which the chromatin was present as fine granules. In addition rounded or oval granular bodies about 15 to 20μ in diameter with a small rounded darkly-staining nucleus, placed eccentrically but not at the margin

of the cell, were present in the most affected areas; some contained clear vacuoles and in occasional cells a single vacuole occupied most of the cell body, but more often several smaller vacuoles were present along with many fine granules. With Mallory's phosphotungstic acid hæmatoxylin a few fine, purple-stained granules were present in the swollen cells, both those with larger and smaller nuclei, but only a small proportion of the granules in the latter type of cell stained in this way. No neuroglial fibres could be seen in the softened areas. There was slight swelling of the cell bodies of the oligodendroglia throughout the section. This appeared to be no greater in the softened area than outside it.

In sections stained for myelin (Loyez method) there was diffuse pallor of the affected region, and under higher microscopic powers many irregular swellings and end bulbs were seen both on the coarser and finer fibres. In addition some irregular granular masses stained black by this method.

In sections stained for axones (Gros-Bielschowsky) all the fibres in affected areas were irregularly beaded with fusiform swellings (figs. 10 and 11), some of the larger fibres formed cocoon-like swellings or irregular varicosities on their course and a few definite end bulbs could be seen. The varicose beaded fibres in the affected area contrasted with the normal straight course of the fibres in unaffected parts of the same section. But in the cortex over the most softened area of white matter some of the fibres ran a wavy course or showed varicosities. Even this part of the cortex showed, however, much less involvement of the axones than the underlying white matter. The neurones in it showed no abnormality.

The changes in this case were considered to be severe and of comparatively short duration.

Case 2.—J. B., aged 54. (Case No. 95/1938.)

Carcinoma nodule in the cortex of the right post-central gyrus about 4 cm. from the mesial margin of the hemisphere (secondary from an oat-celled carcinoma of the bronchus). Severe œdematous swelling of the white matter of the parietal lobe. Post-mortem examination 18 hours after death. In sections stained for myelin the pale zone spread up to the cortex in the most affected areas, but the subcortical U fibres and the line of Baillarger in the cortex were well stained.

Histologically the tissues looked almost areolar, from the separation of the ground substance, and contained many large-bodied cells. Most of these were swollen astrocytes, usually with one, but occasionally with two, nuclei of normal appearance (fig. 19). In addition there was a considerable sprinkling of smaller more rounded cells, with a granular cytoplasm and small darkly-stained nucleus. In some of these the cytoplasm stained grey with hæmatoxylin.

In sections stained by phosphotungstic acid hæmatoxylin there were numerous fibres throughout the swollen area many of which could be traced to the large-bodied astrocytes. Many of the granules in the small granular cells stained purple, but no such granules could be seen in the astrocytes. Loyez myelin method showed irregular varicosities and swellings on the fibres in the œdematous area with many larger fusiform swellings and end globules, as well as granular masses which stained black. The myelin in the overlying cortex looked relatively healthy. In Gros-Bielschowsky sections many fusiform or cocoon-like swellings were seen on the fibres and there were many large end bulbs; a few showed varicosity or feathery irregularity of outline, but the majority appeared to be only slightly affected. In the overlying cortex most of the axones had a normal contour, but some had

irregular thickenings on their course. In the cortex over the swollen area there was a tendency for the neurones, neuroglial nuclei and vessels to separate from the matrix, usually on one side only, an appearance which suggested undue shrinkage. A few of the nerve cells showed slight ischæmic change, but the majority were healthy.

The changes in this case were considered to be of moderate severity and of fairly long standing.

Case 3.—C. K., aged 71. (Case No. 109/1938.)

Carcinoma of the kidney removed five years earlier with secondary deposits in the brain and cerebellum. No operation. Post-mortem examination 12 hours after death. No evidence of excessive intra-cranial pressure. The cerebral tumour was embedded in the inferior surface of the right frontal lobe attached to the dura mater. Swelling of the brain extended from this to the outer surface. In Weigert-Pal sections the white matter of the frontal lobe was very extensively affected, but the corpus callosum stained normally black (fig. 3). On the outer surface of the frontal lobe the subcortical fibres were not preserved. The layer of myelinated fibres in the cortex could still be seen however (fig. 2).

In all sections the tissues had a loosely reticular appearance in the regions affected owing to the presence of large oval spaces which contained a clear colloid matter staining faintly by van Gieson's counter stain. From the large size of the spaces and the absence of nuclei from almost all it appeared that they represented serous exudate into the tissues. The nerve fibres were separated rather than destroyed by them. In addition there were very numerous, more definitely cellular, large bodies, only a few of which had a definite outline. Most of these contained a degenerated nucleus which either stained diffusely and palely or had fine granules of chromatin under the nuclear membrane. Other astrocytes were only slightly swollen; their outline was fairly sharp and more rounded than normal and the chromatin of their nuclei was usually unduly granular. No typical "plump" cells were seen.

In sections stained by phosphotungstic acid hæmatoxylin no neuroglial fibres could be seen in the swollen area, and only a few of the swollen cells contained purple granules. Loyez method showed very great irregularity of contour of almost all the myelin sheaths in the affected area, with many large globules, and a smaller number of small black-staining granules which lay singly in the tissues. The large oval spaces contained no stainable lipoid. In Gros-Bielschowsky sections the larger axones were swollen rather irregularly and a few end bulbs or large fusiform swellings were seen on them. The finer fibres showed many small fusiform swellings, varicosities and end bulbs. In the cortex overlying the swollen area the large pyramidal cells of the 5th layer showed early chromatolysis (axonal reaction) and a few of the smaller neurones had the shrunken cytoplasm and darkly-stained nucleus of ischæmic degeneration. Cells of this kind were scattered irregularly among normal neurones, but in one small area almost every neurone was affected in this manner.

The changes in this case were interpreted as being acute and recent.

Case 4.—E. S., aged 62. (Case No. 35/1937.)

Secondary deposits from a Grawitz tumour of the kidney which had been removed six years earlier. Post mortem 15 hours after death. No evidence of intracranial pressure. The tumours lay in the cortex of the right parietal and

occipito-temporal regions, the larger nodule being near the anterior end of the calcarine fissure. Diffuse œdema extended out from the latter tumour to the external surface of the occipital lobe. The subcortical U fibres were affected in some places under the outer cortex. In the immediate neighbourhood of the tumour there was some vacuolation of the tissues but no stainable substance could be seen in the oval clear areas. Throughout the swollen area all the bodies of the astrocytes were swollen, and some had two nuclei. In some places they seemed to be more numerous than normal. No other change was visible in these areas in sections stained by hæmatoxylin and van Gieson. A diffuse increase in the number of neuroglial fibres could be found throughout the swollen area in sections stained by phosphotungstic acid hæmatoxylin. Loyez method showed separation and beading of the myelin sheaths, but the changes seen were comparatively slight. By the Gros-Bielschowsky method fusiform swellings were seen on a large proportion of the fibres and a few large end bulbs were seen. The changes in this case were interpreted as being subacute.

Case 5.—F. H. (female), aged 60. (Case No. 74/1936.)

Left vertico-frontal endothelioma. Post-mortem examination forty-eight hours after death, which was directly due to pontine hæmorrhage. There was considerable herniation of the hippocampal gyrus through the incisura tentorii, and considerable swelling of the left frontal lobe. In sections stained for myelin there was diffuse pallor of the swollen area running out to the cortex in some places, but in others stopping short at the arcuate fibres.

Histological examination.—This showed distension of all the vessels which were otherwise normal. The cell bodies of all the astrocytes were irregularly swollen to a varying degree. Their outlines were irregular and their nuclei often elongated or irregularly lobed, and many of the nuclei stained palely and diffusely. Occasional bi-nucleated astrocytes were present. A few rounded clear globules which stained a bright orange with van Gieson's counterstain were seen. In the most affected area a narrow zone of pink staining cytoplasm was seen round the oligodendrocytes which otherwise appeared unaffected. Throughout the swollen area there was a diffuse excess of neuroglial fibres which was no longer seen on passing to unaffected areas. Loyez stain showed many large globules of swollen myelin and irregularity of contour of most of the fibres. By the Gros-Bielschowsky method a few end bulbs were seen. There was also some varicosity and irregular thickening of both the fine and coarse fibres, but the changes found by this method were relatively slight. The cortex appeared normal.

The case was interpreted as showing an acute change superposed on a more chronic œdema.

Case 6.—J. S., aged 19. (Case No. 103/1936.)

A large endothelioma had been removed from the right frontal lobe on the day before death. It had involved the precentral convolution. Post-mortem examination thirty-six hours after death. There was considerable erosion of the base and the inner table of the vault of the skull by pressure. There was diffuse swelling of the white matter behind the cavity from which the tumour had been removed. In sections stained with iron hæmatoxylin and van Gieson, the majority of the astrocytes were seen to have greatly swollen irregularly-rounded cell bodies and a marginal nucleus which either stained normally or was paler and more granular

than normal. Some of the astrocytes appeared as a smaller, rounded, rather granular mass of cytoplasm which stained faintly with hæmatoxylin, and had a centrally placed nucleus in which the chromatin was arranged in fine subcapsular granules. Many of the microglial cells had globular, rounded cell bodies with no visible granular inclusions. The oligodendroglia appeared normal. No excess of fibres was seen in sections stained with phosphotungstic acid hæmatoxylin. In Gros-Bielschowsky sections there was an unusual number of cocoon-like and fusiform swellings on the larger axones (fig. 12). The finer fibres showed many varicosities and fusiform swellings. Loyez method showed many larger and smaller swellings on the myelinated fibres and considerable separation of the fibres with many oval lacunæ between them, some of which were filled with the cell bodies of swollen astrocytes.

Many of the changes seen in this case appeared to be of too long standing to have dated from the operation, but some of the more acute changes were no doubt due to this.

Case 7.—F. B., aged 47. (Case No. 105/1938.)

A large left frontal endothelioma had been removed by operation twenty hours before death. At the post-mortem examination it was found that the posterior anastomotic vein, which connected anteriorly with a vein which had been clipped just behind the operation wound in the cortex, had become thrombosed throughout its course. There was, however, no thrombosis of the left lateral sinus. There was considerable œdema of the white matter behind the area occupied by the tumour.

Histologically, in areas near the tumour cell, stains showed moderate swelling of the bodies of all the astrocytes and oval clear areas between the fibres. There was also a considerable overgrowth of neuroglial fibres. By Loyez method there was diffuse pallor of the white matter which diminished on approaching the cortex. The myelinated fibres in the affected area showed very numerous swellings on the course and at the end of fibres. By the Gros-Bielschowsky method an unusual number of end bulbs and fusiform swellings on the course of the fibres was seen.

In the parietal lobe in the territory drained by the thrombosed vein, the appearances were similar. The temporal lobe under the thrombosed vein was much less affected, and apart from a slight degree of ischæmic change in the cortical neurones showed little abnormality. It seemed likely, therefore, that the changes seen near the tumour were associated with pre-existing œdema, and were not related to the venous thrombosis.

Case 8.—G. C., aged 49. (Case No. 81/1938.) *Glioma Cerebri.*

Glioblastoma near the vertex of the left parietal lobe. Post-mortem examination twelve hours after death. Small cerebellar and uncinate pressure cones were present on the left side. The right cerebellar hemisphere was much smaller than the left; this appeared to be a developmental abnormality. There was considerable swelling below and in front of the tumour. In sections stained by Loyez method this area appeared diffusely pale, but the subcortical U fibres were spared in most places.

Histologically, in sections stained by hæmatoxylin and van Gieson, very few normal astrocytic nuclei could be seen. A few cells with a comparatively small well-defined cell body which stained grey with hæmatoxylin had a nucleus of astrocyte size, in which fine granules of chromatin lay under the nuclear membrane

(fig. 16). Many large, irregular, ill-defined clear masses of cytoplasm were seen with a degenerated nucleus which stained very palely and diffusely so that they were scarcely recognisable under low powers (fig. 20). These were considered to be degenerated astrocytes. There was also a smaller number of cells with a rather large lobed degenerated nucleus and a granular cell body which probably represented another form of degeneration of astrocytes. The oligodendroglial nuclei were normal. Many were surrounded by a small, clear zone of cytoplasm. Here and there inside a large myelin swelling could be seen a microglial phagocyte with a relatively large granular cell body and very shrunken nucleus (myeloclast) (figs. 14 and 15).

In sections stained by phosphotungstic acid hæmatoxylin a few wavy irregular neuroglial fibres remained, but the greater number appeared to have broken up and granular chains or short lengths of degenerated fibres could be seen irregularly scattered through the tissues or collected in phagocytic cells. By Loyez method the fibres were extremely irregular in outline with innumerable swellings on their course and terminations and there was also a large number of small collections of black granules of lipoid. The Gros-Bielschowsky method showed a great number of swellings and end bulbs, as well as irregularity of contour of the fibres. By contrast the fibres in the cortex overlying the most affected area of white matter were relatively healthy, although a large proportion of the neurones here, especially those in the deeper layers, showed severe ischæmic changes.

In sections stained by Scharlach R various stages of myelin katabolism could be traced up to the formation of small, rather brightly-staining orange granules, but no red globules or granules could be seen. The widespread degeneration of astrocytes and the severe changes in the axones and myelin in this case indicated its acute nature.

Case 9.—E. E., aged 34. (Case No. 34/1936.)

Glioblastoma of right occipital lobe below and internal to the posterior horn of the ventricle. No operation. Post-mortem examination eighteen hours after death.

The white matter of the right occipital lobe was diffusely swollen and in Weigert-Pal sections stained palely with the exception of the optic radiations and some of the subcortical fibres which stained relatively dark. A wide zone of fibres belonging to the forceps major (i.e. going to the splenium of the corpus callosum), although lying close to the inner margin of the tumour, stained relatively darkly (fig. 5).

In hæmatoxylin van Gieson sections the bodies of the astrocytes were all irregularly but not greatly swollen ; many of their nuclei were swollen and pale, with finely granular chromatin ; some were lobed or reniform, others were rather shrunken and stained more deeply than normal. But a large proportion preserved their normal appearance. The oligodendroglial nuclei were normal, but a narrow crescent of cytoplasm could be seen on one side of most of them. In the overlying cortex a large proportion of the neurones showed ischæmic change, and some of those in the third layer were shrunken and degenerated and were surrounded by granules representing swollen boutons terminaux (incrustation of Golgi network) (fig. 13). No neuroglial fibres could be seen in the swollen areas of white matter.

In sections stained by the Gros-Bielschowsky method there was great irregularity in the outline of the axones and many swellings on their course. In Weigert-Pal sections all the fibres showed large swellings on their course, and a few small collections of free granules of lipoid were also present. The changes in this case appeared to be recent and of a subacute nature.

Case 10.—F. H., aged 56. (Case No. 6/1939.)

A firm glioma was present in the left supramarginal and angular gyri with a cyst in its inferior part. It was adherent to the overlying dura mater. No operation had been performed. The post-mortem examination was made less than twelve hours after death. The white matter internal to the tumour was swollen and in Weigert-Pal sections stained palely. This pale area was limited below by the fissure of Sylvius and internally by the posterior limb of the internal capsule.

In hæmatoxylin van Gieson sections the astrocytes in the swollen area had irregularly swollen cell bodies, sometimes of large size. Their nuclei showed slight degenerative changes; many stained diffusely and palely, in others the chromatin was broken into fine granules. In most of the cells with the latter type of nucleus the cell body was comparatively small and of a greyish colour. A few microglial phagocytes with rather large oval or rounded granular body were seen near the walls of the vessels. A few of the neurones in the overlying cortex showed a slight degree of ischæmic change. None were swollen. The neuroglial fibres were increased in number. The majority preserved their normal outline but a certain number showed granular disintegration, varicosity and other evidence of degeneration.

In Gros-Bielschowsky sections many of the axones were irregularly thickened, others showed fusiform swellings, and end bulbs were very numerous.

In Weigert-Pal sections many irregularly thickened sheaths were found with lateral spicules or globules, and all the thicker sheaths had large fusiform swellings on their course. Most of the finer fibres had broken down into a detritus of fine lipoid granules.

By Loyez method the alterations in the myelin seemed rather less acute, but an enormous number of fusiform and irregular swellings was seen as well as many black-staining free granules. This section passed through a less severely affected area than that used for the Weigert-Pal method.

There seemed to be an old standing gliosis in this case with more acute changes superimposed.

Case 11.—A. L., aged 40. (Case No. 8/1939.)

A rounded mass of glioma spanned the anterior part of the right Sylvian fissure invading the upper surface of the temporal pole and the overlying frontal lobe. No operation was performed. The post-mortem examination was made fourteen hours after death. There was diffuse swelling of the right hemisphere behind the tumour extending backwards beyond the splenium of the corpus callosum. At this level Weigert-Pal sections showed diffuse pallor of the white matter with relative sparing of the optic radiations. The splenium of the corpus callosum was of the normal black colour.

In sections stained with hæmatoxylin and van Gieson all the astrocytes were swollen with normal nuclei and an asteroid cell body giving rise to fine processes. Bi-nucleated astrocytes were not seen. No other abnormality was seen either in the white matter or the overlying cortex. There was a considerable excess of neuroglial fibres in the affected area of white matter.

In Weigert-Pal sections the myelin sheaths showed a certain amount of beading, but this was slight by comparison with that seen in most of the cases. The changes in the axones in Gros-Bielschowsky sections were also slight although fusiform swellings and end bulbs were fairly numerous.

This case showed only slight, and apparently early, changes.

Case 12.—J. H., aged 45. (Case No. 11/1939.)

A cellular localized astrocytoma composed of pyriform and fusiform cells was present in the upper part of the left parietal lobe. A craniotomy had been performed less than twenty-four hours before death. At the post-mortem examination which was made thirty-six hours after death a well-marked uncinate pressure cone on the left side with bruising of the right crus was found. There was a moderate degree of swelling of the white matter of the parietal lobe under the tumour and this in Weigert-Pal preparations showed as a diffuse pallor of staining with preservation of the subcortical U fibres and the corpus callosum.

In sections stained with hæmatoxylin and van Gieson the bodies of all the astrocytes were moderately swollen : their nuclei were normal or slightly enlarged ; a few were elongated or uniform. An occasional cell had two nuclei. A narrow crescent of cytoplasm could be seen round many oligodendroglial nuclei. The neurones in the overlying cortex were healthy. There was an excess of neuroglial fibres amounting to a fibrous gliosis throughout the affected area (fig. 21); this disappeared as the subcortical zone was reached.

In Weigert-Pal preparations the number of myelinated fibres seemed greatly reduced, and those that were present had many large swellings on their course. In Gros-Bielschowsky sections also there was a poverty of axones and those that were present showed considerable irregularity of contour. Large cocoon-like swellings on the thicker axones were very abundant in this case.

The changes in this case were considered to be of considerable duration. Although only slight changes were demonstrated by nuclear and cell stains, they were associated with severe degeneration of the nerve fibres and with great neuroglial sclerosis.

Summary.

A histological study was made of 28 cases of cerebral œdema related to cerebral tumours. In these cases œdema was found to be constantly associated with definite histological changes of the following kinds:—

(1) The myelin in the centrum ovale stained palely, but that in the large commissural tracts, such as the corpus callosum, the internal capsule and the optic radiations, was relatively or absolutely normal. The pallor of staining was due partly to separation of myelinated fibres, but also to degeneration of the myelin, which in severe cases might be broken up into granules and globules.

(2) The axones were less affected than the myelin, but showed degenerative changes such as beading, irregularity of contour, end bulbs and cocoon-like swellings on their course. The axones in the cortex were relatively or absolutely normal.

(3) The astrocytes in the white matter were always swollen. In the less acute cases they appeared as Nissl's "plump" astrocytes and there was an excess of neuroglial fibres. In more acute cases the astrocytes showed clasmatodendrosis and various degenerative changes in the nuclei.

(4) The microglial cells in the affected areas were mobilized in the

early stages of phagocytosis of lipoid. The oligodendroglial cells were relatively normal.

(5) Vascular congestion was only found in cases of endothelioma. There was no evidence of endothelial proliferation or of distension of the Virchow Robin spaces. In most cases the vessels appeared to be unaffected.

(6) The neurones in the overlying cortex might show some ischæmic degeneration in severe cases. Both the myelin and axones were relatively unaffected in the cortex and subcortical zone.

These changes were considered to be due to anoxia of the tissue of which the chief cause was probably the excess of interstitial fluid, but venous obstruction and reduction of the size of the capillary bed may have also played some part in its production.

The most severe and acute changes were found in cases of rapidly growing tumours (secondary cancers and glioblastomas). Changes of a more subacute type might occur in association with tumours of slow growth (endotheliomas and astrocytomas).

In these cases no sharp distinction can be made between "brain swelling" and cerebral œdema; what has been described as œdema is a more severe degree of the same process as "brain swelling." The general "brain swelling" which occurs in general infections and intoxications may be associated with quite different histological changes from those found in association with cerebral tumours.

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LEGENDS FOR PLATES.

PLATE III.

FIG. 6.—*Case 9.* Right occipital glioblastoma. The myelin sheaths in the most œdematous area are very scanty and those present show many bulbous swellings on their course or at their terminations. (Weigert-Pal counterstained alum carmine.)

FIGS. 7 & 9.—*Same case as fig. 1.* Secondary nodule from bronchial carcinoma. There is extreme loss of myelin sheaths in the œdematous area behind the tumour. Much of the myelin has broken up into fine granules of lipoid. The sheaths that remain are irregularly beaded with larger and smaller swellings. (Weigert-Pal counterstained carmine.)

FIG. 8.—*Case 3.* Secondary nodules in right frontal lobe from a renal carcinoma. The myelin sheaths are irregularly swollen and many granules of lipoid lie free in the tissues. (Weigert-Pal counterstained alum carmine.)

PLATE IV.

FIG. 10.—*Case 1.* Secondary nodule from bronchial carcinoma. Numerous end bulbs are seen on the finer fibres. (Gros-Bielschowsky.)

FIG. 11.—*Case 1.* Large skein-like end swellings are seen as well as swellings and end-bulbs on the fine fibres. (Gros-Bielschowsky.)

FIG. 12.—*Case 6.* Right frontal endothelioma removed on day before death. Cocoon-like swelling on a fibre in the œdematous area behind the tumour. (Gros-Bielschowsky.)

FIG. 13.—*Case 9.* Right occipital glioblastoma. Neurones from third layer of cortex on the outer surface of the occipital lobe. The central neurone shows severe ischæmic change, with staining of the swollen *boutons terminaux* round it. (Hæmatoxylin van Gieson.)

PLATE V.

FIGS. 14 & 15.—*Case 8.* Glioblastoma of left parietal lobe. Myeloclasts are seen inside swollen myelin sheaths. (Iron hæmatoxylin van Gieson.)

FIG. 16.—*Case 8.* A slightly swollen astrocyte with a pale nucleus containing fine subcapsular granules. (Iron hæmatoxylin van Gieson.)

FIG. 17.—*Case 8.* Microglial phagocyte containing fine granules of lipoid lying beside a capillary. (Iron hæmatoxylin van Gieson.)

FIG. 18.—*Case 5.* Fronto-vertical endothelioma. A swollen bi-nucleated astrocyte is seen with much overgrowth of neuroglial fibres. (Mallory's phospho-tungstic acid hæmatoxylin.)

FIG. 19.—*Case 2.* Secondary nodule from a bronchial carcinoma. Two swollen astrocytes are seen one of which has a multi-lobular nucleus. (Iron hæmatoxylin van Gieson.)

FIG. 20.—*Case 8.* Four swollen astrocytes with pale diffusely-stained nuclei are seen among the darkly-stained oligodendroglial nuclei. (Iron hæmatoxylin van Gieson.)

FIG. 21.—*Case 12.* Astrocytoma of left parietal lobe. Diffuse gliosis in the œdematous area remote from the tumour. (Mallory's phosphotungstic acid hæmatoxylin.)

PLATE III.

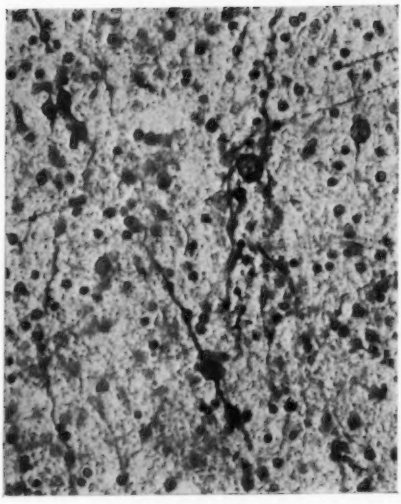

FIG. 6.

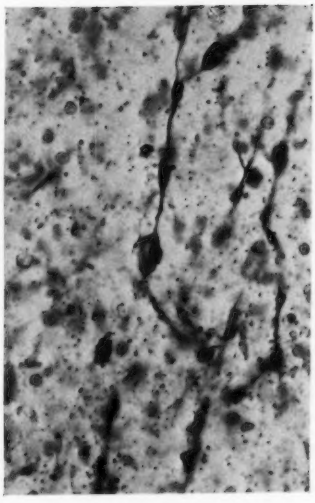

FIG. 7.

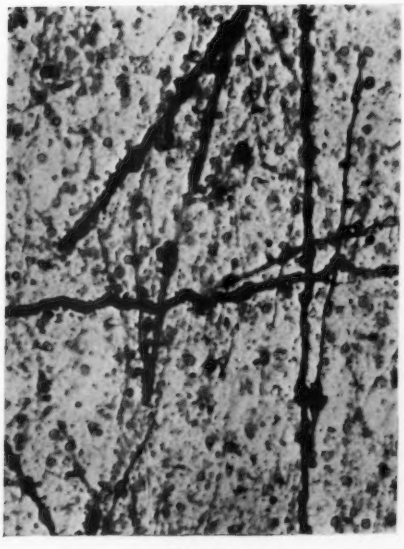

FIG. 8.

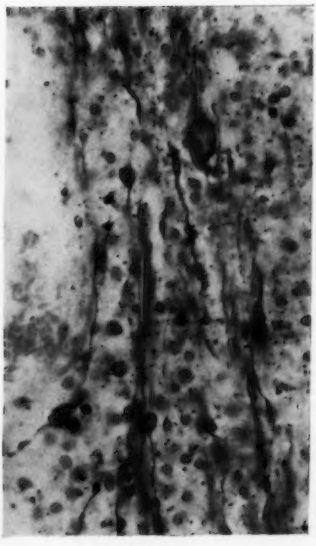

FIG. 9.

To illustrate article by J. G. Greenfield.

PLATE IV.

FIG. 10.

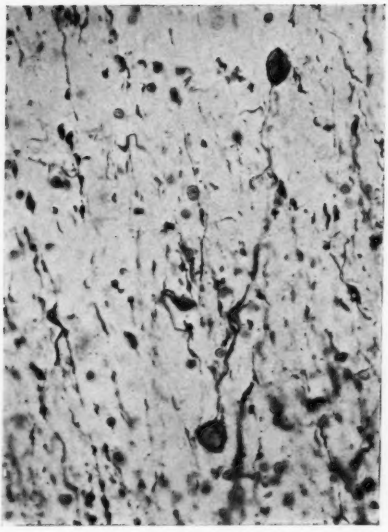

FIG. 11.

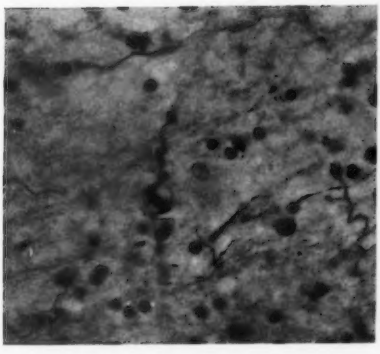

FIG. 12.

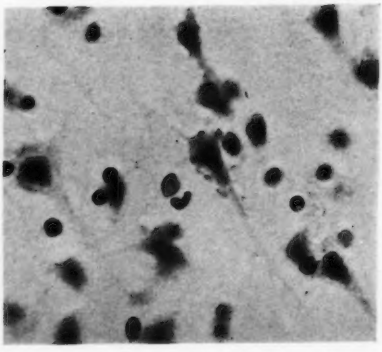

FIG. 13.

To illustrate article by J. G. Greenfield.

PLATE V.

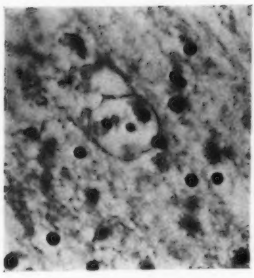

FIG. 14.

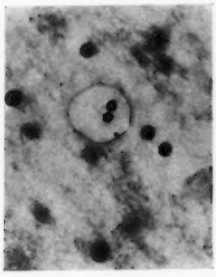

FIG. 15.

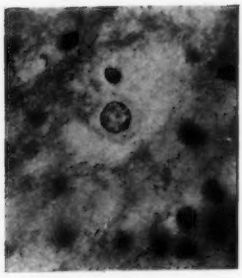

FIG. 16.

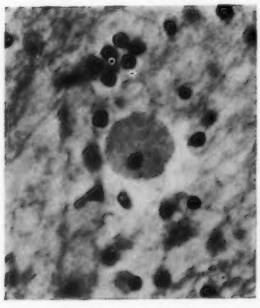

FIG. 17.

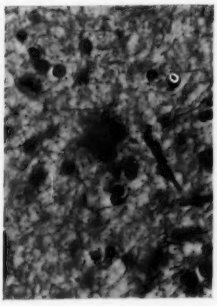

FIG. 18.

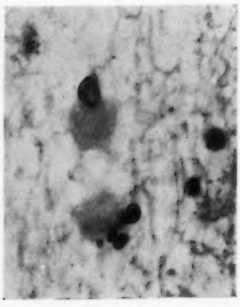

FIG. 19.

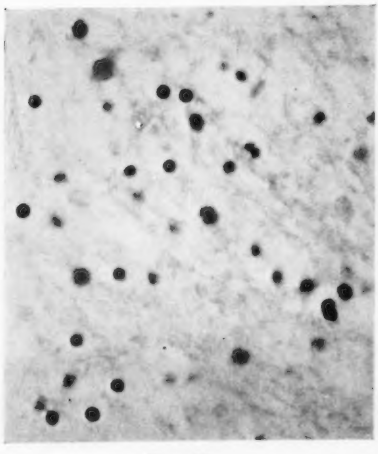

FIG. 20.

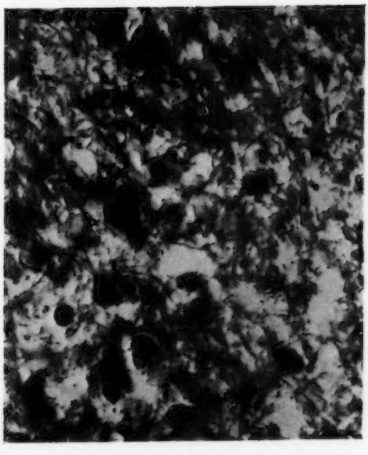

FIG. 21.

To illustrate article by J. G. Greenfield.

THE POTASSIUM CONTENT OF MUSCLE IN DISEASE.

BY J. N. CUMINGS.

(From the Biochemical Laboratory, National Hospital, Queen Square, London.)

THE potassium content of human voluntary muscle has received very little attention; more especially is this so in disease processes affecting muscles. Leulier, Pommé and Delaye (1931) and Leulier and Pommé (1932) showed that in a few common nervous and muscle disorders, such as progressive muscular atrophy, there was a normal potassium content of the affected muscles.

The present paper records the potassium content found in muscles in a variety of diseases, with special reference to dystrophia myotonica and myasthenia gravis, in which conditions no previous investigations of a similar nature appear to have been made. The effect of the administration of prostigmin upon the muscle potassium has also been studied.

METHODS AND MATERIAL.

Muscle was obtained in almost every case by biopsy from an affected area and the potassium content estimated as previously described (Cumings, 1939). The effect of prostigmin upon the muscle potassium was determined in some cases of myotonia and myasthenia gravis. In such patients, after muscle had been removed, prostigmin (mgm. 1) was administered subcutaneously, and after half-an-hour another piece of muscle removed. The serum potassium in one case of myasthenia gravis was also examined before removal of any muscle and again after the second piece had been taken.

RESULTS.

The cases in which normal potassium contents in affected muscles were found are given in Table I.

Abnormal muscles containing a low potassium concentration are seen in Table II. This group consists of muscles containing a large excess of fat (pseudo-hypertrophic muscular dystrophy) or of fibrous tissue (peroneal atrophy) and of muscles from patients with myotonia.

Lastly, in Table III are shown the results from five patients with myasthenia gravis in whose muscles there was a raised potassium content.

TABLE I.

Name	Disease	Potassium in grm. % of wet weight	Potassium in grm. % of dry weight
C.	Progressive muscular atrophy ...	0·34	1·18
G.	,, ,, ,, ...	0·23	0·93
P.	Simple atrophy	0·287	0·966
K.	Charcot-Marie-Tooth	0·21	0·954
D. K.	Myositis	0·263	1·13
Gr.	Wasting associated with cerebral tumour	0·22	0·99
L.	Peripheral neuritis, right side ...	0·27	1·15
	,, ,, left side ...	0·288	1·49

TABLE II.

Name	Disease	Potassium in grm. % of wet weight	Potassium in grm. % of dry weight
W.	Pseudo-hypertrophic muscular dystrophy	0·102	0·204
M.	Peroneal atrophy, right side ...	0·132	0·402
	,, ,, left side ...	0·085	0·229
L.	Marked atrophy with fibrous tissue replacement	0·23	0·55
F. S.	Myopathy with marked fibrosis ...	0·195	0·369
V.	Myotonia	0·14	0·532
B.	,, ...	0·302	0·454
S.	,, ...	0·19	0·74

TABLE III.

Name	Disease	Potassium in grm. % of wet weight	Potassium in grm. % of dry weight
Mrs. W.	Myasthenia gravis	0·376	1·522
Mr. B.	,, ,,	0·697	2·61
Mrs. B.	,, ,,	0·568	2·28
Miss H.	,, ,,	0·49	2·33
Mr. D.	,, ,,	0·364	1·504

Results of Prostigmin Administration.

Muscles from two normal subjects, two cases of myotonia and two cases of myasthenia gravis were investigated. The results are shown in Table IV. The potassium content in dry muscle only is given in order to show the

results more clearly, but the findings were comparable in both dry and wet weight of muscle.

TABLE IV.

Name	Disease	Potassium in grm. % of dry weight	
		Before prostigmin	After prostigmin
L.	Normal	1·23	1·49
I.	"	1·12	1·12
B.	Myotonia	0·454	0·606
S.	"	0·74	1·47
H.	Myasthenia gravis	2·33	1·0
D.	" "	1·504	0·613

Discussion.

It has been shown that normal muscle contains a potassium content that may vary from 0·2 to 0·35 grm. per cent. of wet weight and 0·8 to 1·2 grm. per cent. of dry weight (Cumings (1939)) and it is seen that in all except a very few diseases there is a normal muscle potassium content. Muscles with gross replacement by fibrous tissue or fat show a marked diminution in potassium content and this is to be expected, as Gersh (1938) has shown that the potassium is contained in the muscle fibre and that there is practically none in the interstitial tissue.

The most marked exception to normal potassium content occurred in muscles from myotonia and myasthenia. In myotonia there was a very marked diminution in potassium content and this cannot be accounted for by the lack of muscle fibres, for although this did exist, the potassium was estimated in relation to weight of muscle examined. Also macroscopic and microscopic examination showed practically no increase in fibrous tissue. There has also been shown to be a diminution in muscle potassium content in experimental nutritional muscular dystrophy in animals (Fenn and Goettsch, 1937).

The very marked increase in potassium content in muscles from cases of myasthenia may be of considerable importance.

The effect of prostigmin on muscle potassium was interesting. Muscles from normal patients showed no appreciable alteration in potassium content after the administration of prostigmin. Muscles from cases of myotonia and of myasthenia showed after prostigmin an approach to the normal muscle potassium level. Concurrently with the return to a normal potassium level there was a return to normal muscle function in patients with myasthenia gravis. Patients with myotonia showed no clinical

improvement, either as regards the myotonia or their normal muscle function, although the potassium content approached the normal, and this was not surprising, as all the muscles showed some signs of atrophy.

One case of myasthenia (Table IV, D) showed a rise in serum potassium after prostigmin. The resting level was 25·2 mgm. per cent. and this rose to 36·47 mgm. per cent., so that it appeared that the potassium liberated from the muscle passed into the blood.

The method of action of prostigmin upon the muscle potassium and the fate of the liberated potassium are now being investigated.

Summary.

The potassium content in muscles in various nervous and muscle disorders has been estimated, especially in muscles in myotonia, in which there is a low potassium level, and in myasthenia, in which a high potassium level is recorded.

Prostigmin has been shown to produce a rise in the potassium level in muscles from cases of myotonia, and a fall in potassium in myasthenic muscles.

It is with pleasure that I thank the Staff of the National Hospital, Queen Square, for allowing me to utilize material from patients under their care.

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SEVERE DEMENTIA ASSOCIATED WITH BILATERAL SYMMETRICAL DEGENERATION OF THE THALAMUS.[1]

BY K. STERN.

(From the National Hospital, Queen Square, London.)

THE following is the report of a case for which no analogy could be found in the literature. Apart from this interest, which is offered from the point of view of mere peculiarity, it appears to throw more light on the question of disturbance of thalamic functions, and to contribute to the morbid anatomy of the thalamus.

CLINICAL HISTORY.

The patient, a man of 41 years, was admitted to the National Hospital under Dr. F. M. R. Walshe on February 9, 1938.

The patient's history was obtained from his wife. His father and mother were alive and well. One brother and one sister were alive and well; none had died. There was no history of nervous or other disease in the family. The patient's wife was well.

Previous to the present illness he had always been healthy, active and energetic. His wife knew of no previous illnesses, accidents or operations. During the war he was in Mesopotamia and India for four years; he was in hospital once while serving abroad, but the nature of this illness was not known.

Until May, 1937, nine months before his admission to the hospital, he was always active, healthy, and alert, working in a chemist's shop. In May he gradually became "run down," complained of pain in his left shoulder and "was felt to be in need of a rest." In July he was becoming more inert, was always licking his lips and complaining of his mouth being dry. He developed marked thirst and polyuria, which persisted for two months. He also became very drowsy. He fell asleep after every meal, slept heavily at night, and was difficult to wake in the morning.

In August, 1937, he had to give up work, and subsequently he gradually lost his speech. He used to be a good talker, but in the last six months before admission he had steadily become more silent and his voice had become weaker. He did not use wrong words, nor was there any apparent difficulty in expression; it was simply that he spoke less and less. His understanding was impaired: "when asked to pass one thing he passed something else." He became unable to write and could scarcely read, though he looked at the picture papers.

He grew slowly and steadily worse, becoming very slow in all his movements and completely inert. There was no obvious depression, no tremor or paralysis

[1] This work was carried out while holding the Kathleen Schlesinger Research Fellowship.

of the limbs. His mind wandered and he often made remarks with no bearing on the conversation. He talked nonsense and described himself as doing things which he was known not to have done. His memory was very poor, and he did not seem to know that he was ill. He appeared to think he was still at work, and in bed performed the actions appropriate to his work, for example, the dispensing of a prescription.

He had no headache or vomiting, neither "fits" nor attacks of unconsciousness. Squint, diplopia, or loss of vision were never observed. When he was admitted to hospital he had no polyuria; he had never shown any sign of incontinence. He was able to walk about two miles, but he was very slow and rather unsteady. His legs tired easily and he shuffled; there was, however, no dragging of one leg or any marked deviation, and he had not fallen. His general health was good. He ate well, chewed and swallowed normally. He had lost a little weight. Digestion was normal. Cough or dyspnœa were never observed.

On examination he presented the picture of a fairly healthy-looking, well-built man. His speech and articulation were normal, apart from the content of the former. He had a worried, rather sullen and stuporose expression. He was extremely restless and constantly shifted about in bed, rearranging the sheets, making as if to get up, rubbing his head and face. There were numerous mannerisms, such as pointing in a grotesque way, sucking his lips, and a striking tendency to repeat actions and words once elicited. After the tongue had been put out, its protrusion was for some time the invariable response to any other command. He ignored the attempt at examination and repeatedly buttoned up his pyjamas or turned on his side—not, however, in the manner of an active resistance, but as if he did not recognize what was wanted. There was no obvious lack of comprehension, but he was extremely uncommunicative and frequently ignored any question or command. There was a striking tendency to repeat the question, or to answer by a simple rearrangement of the questioner's words. The whole mental atmosphere was weird, uncanny and crafty.

Specimens of Conversation.

What is your name?	(Answered correctly.)
How old are you?	"Eighteen." (Ten minutes later said "eight or nine.")
Where are you?	"Just thinking where I'd like to be."
How long have you been here?	"Four or six months."
Where were you before? ...	"The room very similar to the other one, but perhaps a different build."
What is the date?	"Jan. 25 or 26, I think."
What year?	"203." (Persists in 203 to repeated questioning.)
Who is the King?	"King George."
What number?	"209."
When did the War begin? ...	"209."
How long did it last?	"209."
When did it finish?	"About 209—I can't think about that like I do about other things."
What do you think of?	"Scent of spray."
What are you interested in? ...	"Everything."
What are you most interested in?	"Most things."
What most of all?	"Right things most."

Cranial nerves.—The optic discs were of normal colour and the edges were sharp. The vessels and the retinæ were normal. The pupils were of moderate size, equal, central and circular. They were fixed to light and also on convergence, which was very poor. The external ocular movements were full in all directions, without strabismus or nystagmus. There was no ptosis, enophthalmos or exophthalmos. The jaw opened and closed normally. The corneal reflexes were brisk and equal. There was a slight left lower facial weakness at rest or on movement. There was no tremor of the mouth or eyelids. The palate rose in the mid-line. The tongue was protruded in the mid-line ; there was no tremor, wasting or fibrillation.

Upper limbs.—The power was good and equal in all muscle groups. There was neither rigidity nor tremor, wasting nor fibrillation. There was no gross ataxia, but he introduced perverse movements into co-ordination tests.

Lower limbs.—There was no wasting or weakness. Frequent movements and rigidity of a voluntary order made the examination difficult. It could, however, be stated with certainty that there was no ataxia.

Sensation could not be tested.

Reflexes.—All tendon-jerks were symmetrical and very brisk, especially in the upper limbs. The abdominal reflexes were sluggish and equal. The plantar responses were indefinite owing to voluntary posturing and withdrawal.

The heart and chest were normal on examination.

Lumbar puncture.—The pressure was 160 mm., and the final pressure 140 mm. The fluid was clear and colourless. No cells were seen. The amount of protein was 0·020 per cent. Nonne-Apelt and Pandy reactions were negative. Lange's test did not show any change. The Wassermann reaction was negative in the cerebrospinal fluid and in the blood.

A radiogram of the skull did not reveal any sign of intracranial growth.

On February 22, 1938, a bilateral ventricular puncture was performed. The cortex seemed further away from the dura than in normal cases. Both ventricles were entered without difficulty at an equal and normal depth. The ventricular pressure was not raised. The ventricular fluid did not show any abnormalities on routine chemical and microscopical examinations.

On numerous occasions during the period between his admission to hospital and his death, the patient showed the following phenomena.

Sucking: with eyes open.—If the examiner's finger, or a pencil, were brought close to either angle of the mouth, the moment this object came into the patient's view a pursing movement of the lips was made on the side from which the object approached. The protruded lips parted and the object was seized between them and sucking movements followed. This was as readily elicitable from one angle of the mouth as the other, and could be repeated many times in quick succession.

With eyes closed.—The lip protrusion and sucking occurred at once if the stimulating object made contact with one corner of the mouth.

Grasping.—Grasping movements, of some force and marked rapidity, were elicitable from either hand.

With eyes open.—If the examiner's finger—within the patient's view—were approached to the gap between the thumb and index finger of the patient's hand, a grasping movement at once was made. On contact these digits closed round the examiner's finger. Contact of the examiner's finger with the palm of the patient's hand led to quick closure of the latter.

With eyes closed.—Contact alone—as described above—elicited these movements.

Tonic grasping.—Any attempt to withdraw the examiner's finger from the patient's grasp—unless so carefully and slowly attempted as to avoid all movement of, or fresh contacts with, the patient's hand, evoked strong tonic grasping. The effective stimulus appeared to be stretching of the finger flexors.

During this period the patient was fatuous and incapable of sustained attention. The sucking and the grasping movements appeared to be carried out automatically and without special attention on the patient's part once the appropriate stimulus was provided. Even when he lay drowsy and with eyes closed sucking and grasping movements were elicitable once the necessary contact with the stimulating object was made.

These phenomena persisted until the final state of coma.

Summary of Clinical History.

A man of 40 developed rather rapidly the picture of a severe organic dementia with drowsiness. The dementia was a general one with gross lack of memory and orientation, a tendency to perseveration, combined with considerable changes of personality, such as inertia and a complete lack of initiative. From the statement that he spoke of "doing things which he was known not to have done" it appeared that the gaps of memory were filled by confabulations, a phenomenon familiar in Korsakoff's syndrome. One the other hand, focal symptoms such as aphasia apraxia, and agnosia, appeared to be absent. The only neurological signs were the loss of the pupillary reflex to both light and convergence, the sucking reflex, and the grasping phenomena.

In view of the rapid mental deterioration with signs of severe cortical impairment combined with loss of the pupillary reflex, although not of a true Argyll-Robertson character, the diagnosis of general paresis seemed obvious. This, however, could not be confirmed by serological examination. There were no clinical signs of arteriosclerosis or of arterial hypertension ; thus a diffuse vascular disturbance could also be excluded.

The remaining possibilities were an intracranial neoplasm, or some rarer condition such as presenile dementia (Alzheimer's disease) or circumscribed cortical atrophy (Pick's disease). These two last-named diseases have never been observed accompanied by disturbance of the pupils, whereas it is known that ocular signs may occur in supratentorial tumours (Collier, 1904). Therefore the picture of severe mental deterioration accompanied by very marked grasping phenomena, and yet unaccompanied by signs of raised intracranial pressure, led finally, by the exclusion of all the other possibilities, to the diagnosis of a neoplasm of one or both frontal lobes. The bilateral ventricular puncture, however, did not add anything to confirm this diagnosis. Thus, when the patient lapsed into the final stages of coma, the diagnosis had not been sufficiently clear to justify an exploratory craniotomy.

Post-mortem.—The body of a rather thin middle-aged man with recent parietal burr holes for ventriculography. Brain and spinal cord only removed. No thickening of skull ; dura quite lax. No herniation. Meninges and vessels normal. No evidence of cerebral atrophy. Brain weight (unfixed) 1,270 grammes.

Microscopical examination.—Blocks from the cerebral hemispheres, from the cortex, basal ganglia, lower brain-stem, medulla oblongata, and the cerebellum, and spinal cord were examined in frozen and in celloidin sections. The methods of Weigert-Pal, Nissl, Bielschowsky, v. Braunmühl, Bielschowsky-Gros, Herxheimer (scharlach R), Wilbur Smith (myelin sheaths), Holzer, Mallory (phosphotungstic acid hæmatoxylin), and Van Gieson were applied. Brodmann's areas 1, 3, 4, 6, 8, 9, 10, 11, 17, 18, 19, 23, 24, large blocks from the temporal, parieto-occipital and occipital regions, and blocks from the hippocampal region of both hemispheres were examined partly with Nissl's method and partly with myelin-sheath preparations on ordinary celloidin (Smith and Quigley, 1937). The right thalamus was cut completely in serial coronal sections (15 μ), and each fifth section stained with thionin. Of the left thalamus, parts had already been used for Weigert-Pal and frozen sections in routine examinations, therefore only two large horizontal blocks of the left basal ganglia could still be used for serial sections (15 μ), every fifth section being stained with thionin.

The meninges were normal everywhere, except for a perivascular collection of round cells in the temporal region. The vessels were normal everywhere. In the left putamen some of the perivascular spaces were enlarged and contained a few fat granule cells, the vessels themselves being perfectly normal.

The cortex showed diffuse pathological changes which were accentuated in certain areas and less distinct in others. They were nowhere focal or sharply circumscribed and so could not be detected with the lowest powers. These changes were not very characteristic ; there was a certain degree of lipoid atrophy of ganglion cells with a considerable amount of glial overgrowth in which all kinds of glia cells took part. This change was most marked in the lower and middle layers of the cortex. The arrangement of glia cells was loose and irregular, the single elements being rather swollen ; thus the gliosis appeared to be rather recent. The degree of these changes varied from a slight gliosis, such as could be encountered in any brain after intercurrent internal disease, to a conspicuous degree of cell proliferation. The cyto-architecture of the cortex, however, was nowhere disturbed. The areas mainly affected were the posterior parietal region and the temporal region, and small parts of the granular frontal cortex, on the whole more on the right than on the left side. The greater part of the granular frontal cortex, however, was free. The posterior limbic region (area 23) was affected on the left side.

Fat staining (scharlach R) showed a considerable amount of lipoid degeneration of ganglion cells. Numerous capillaries all over the examined parts of the cortex showed fat granule cells and fat-containing endothelial cells.

The white matter presented the picture of an even, dense, cellular gliosis. Here, too, some capillaries showed fat granule cells. In one area near the posterior part of the corpus callosum there was a large perivascular collection of fat granule cells. In myelin preparations (Weigert-Pal, Wilbur Smith) the subcortical white matter and the centrum semiovale were normal. The axis cylinders (Bielschowsky-Gros) appeared normal. In glia fibre preparations (Holzer) there were numerous large fibrous astrocytes distributed all over the white matter and over the inferior layers of the cortex. There were also monster glia cells. Those cells were arranged loosely

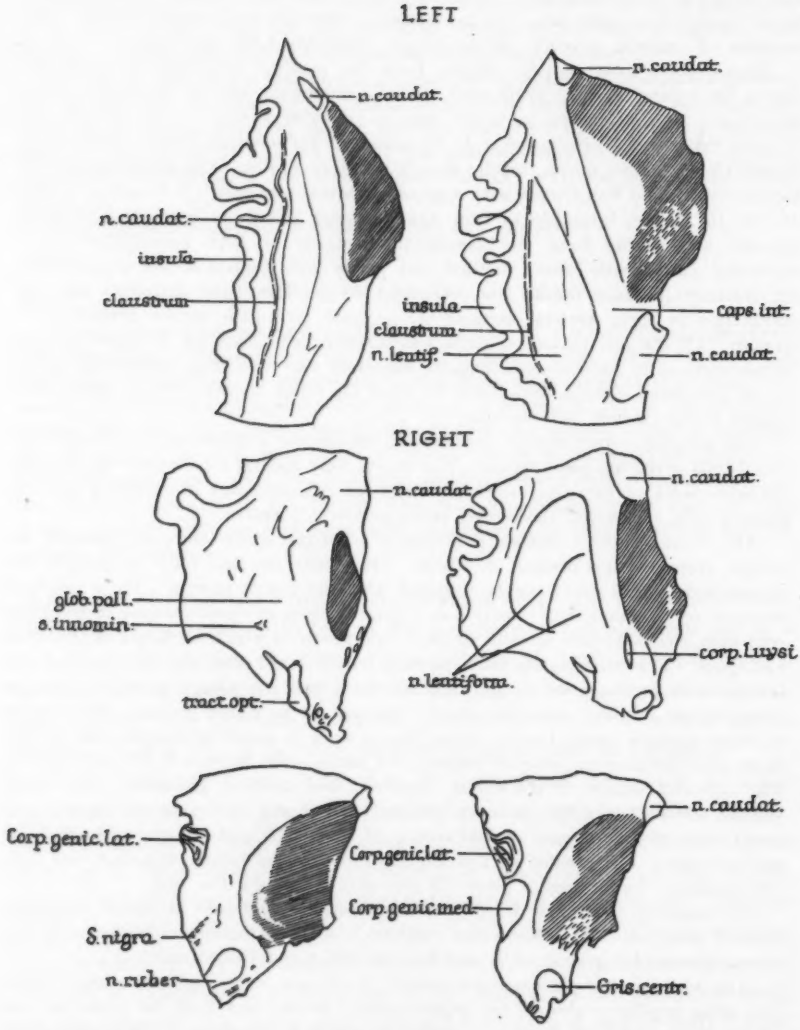

FIG. 2.—Representative sections from basal ganglia of both sides in camera lucida drawings. The left basal ganglia were cut in horizontal sections (upper 2 pictures). The degenerated areas are shaded.

or in small foci, and there was no dense fibre network as one might expect from the degree of cellular gliosis.

Basal ganglia.—The most striking pathological finding in this case presented itself in the thalamus on both sides. There were areas which were completely devoid of ganglion cells (fig. 1), and others in which a comparatively few sclerotic ganglion cells were scattered within a dense and even gliosis. The preserved areas in the right thalamus were as follows—(fig. 2) the ventral and arcuate nucleus (mainly ventricular nucleus b and c of Monakow), (fig. 3) cells of the zona reticulata, most of the irregularly scattered medial "hyperchromatic" nuclei (n. reuniens of Malone, mid-line nuclei of Le Gros Clark), (fig. 4) including the massa intermedia, and both the lateral and medial geniculate bodies. The anterior nucleus, the medial nuclei in the proper sense, the centro-median nucleus, and the lateral nuclei had disappeared. The habenular ganglion was preserved. On the left side, as far as could be seen from the remaining blocks, the picture was the same. Here, in an area corresponding to one of the medial nuclei, a considerable collection of fat granule cells and macrophages was found. The medullary laminæ, especially the external one, showed a marked gliosis which made them stand out on naked-eye inspection. In Bielschowsky-Gros preparation a regular network of axones was still preserved in areas which were devoid of all ganglion cells (fig. 5). Preparations with phosphotungstic acid hæmatoxylin (Mallory) demonstrated the dense and even distribution of fibrous astrocytes and monster glia cells over the whole of the degenerated area. In marked contrast to this picture silver stains of the mesodermal elements (Klarfeld-Achuccaro) did not reveal any form of reaction. The borderline between diseased and preserved parts in the thalamus was sharply defined.

Apart from a considerable amount of lipoid pigment in ganglion cells, the remaining parts of the basal ganglia (corpus striatum, globus pallidus, corpus subthalamicum) and the preserved areas of the thalamus were normal. The hypothalamic nuclei, the mid-brain, and the examined parts of the lower brain-stem were normal, except for a certain amount of gliosis with neuronophagia in the superior colliculi and a complete atrophy of considerable sectors of the inferior olive on both sides. This atrophy was somewhat symmetrical and affected the medial parts of both the ventral and dorsal bands.

Trial sections from various areas of the cerebellum (Nissl, Bielschowsky-Gros, Van Gieson) and from various levels of the spinal cord (Nissl, Weigert-Pal) were normal. The pituitary gland was normal.

Discussion of Pathology.

Reviewing the histopathology of this case one can state that all the findings, the main lesion in the thalamus, and the less conspicuous findings in the cerebral cortex and inferior olives, have one essential point in common—viz. parenchymatous degeneration with consequent glial reaction. An inflammatory condition may be excluded from the findings both in the meninges and in the central organ, quite apart from the clinical picture.

There are various possibilities as to the nature and origin of these parenchymatous lesions. At first sight one might be inclined to think of

a vascular basis for the entire process. The extra- and intracerebral vessels, however, were normal, and the clinical picture itself makes it unlikely that the case was one of arterial hypertension with histologically normal arteries. It is true that the slight diffuse gliosis in the cortex and the sector atrophy of the inferior olives, both of which were accompanied by a corresponding gliosis, belong to the type of lesions encountered in diffuse vascular disease such as arteriosclerosis. A closer study of the thalamic lesions, however, is against the assumption of an ischæmic lesion. The fact that in the areas of complete disappearance of ganglion cells a network of fine axis cylinders obviously of afferent neurons was preserved, excludes this possibility. A degree of ischæmia sufficient to destroy all the nerve cells of an area and to provoke a vast glial overgrowth, and yet on the other hand not sufficient to destroy axis cylinders in the same area, is inconceivable. Moreover, an ischæmia of such a degree would in every case be followed by a glial *and* mesodermal reaction; the complete absence of capillary proliferation is therefore to be regarded as further evidence against an ischæmic lesion. Apart from these features, which exclude with certainty a vascular origin of the lesion, there are others which would make it extremely unlikely even if nothing else were known. Firstly, the site of the lesion does not coincide with any known area of vascular supply; e.g. the same arterioles which supply the medial thalamic nuclei ("artères thalamo-perforées," Foix and Hillemand, 1925) supply also the zona incerta and the anterior part of the red nucleus both of which were intact in the present case. Secondly, the border of the lesion coincides exactly with the border of the thalamus towards the internal capsule and the caudate (fig. 1). Another feature, quite uncommon in vascular diseases of the basal ganglia, is the fact that the lenticular nucleus and the internal capsule are intact, and that the process is confined to the thalamus in an apparently symmetrical manner.

Having thus excluded inflammatory and vascular processes the range of possibilities is considerably lessened. The main question that remains is whether the degeneration is a retrograde one, such as is observed after damage to the thalamo-cortical neuron by a cortical or subcortical lesion. The histological picture, viz. the simple disappearance of ganglion cells and purely glial overgrowth, and the preservation of such functional units as the ventral thalamic nucleus and the geniculate bodies, makes this suggestion a likely possibility.

Before going into this question any further it is necessary to discuss the pathological changes in the cortex and white matter observed in this case. The clinical picture was one of severe subacute presenile dementia;

syphilis could be excluded, and the possibilities of a frontal lobe tumour, a circumscribed cortical atrophy (Pick) or a diffuse presenile degeneration (Alzheimer) remained. Pick's disease is characterized by an atrophy of certain parts of the cortex, most frequently in the frontal or temporal lobe, which is visible to the naked eye, and which produces a considerable diminution of the weight of the entire organ. Even in cases at an initial stage of the disease the circumscribed atrophy is macroscopically visible, at least after ablation of the meninges (v. Braunmühl, 1930). Histologically the atrophy always begins in the upper three layers of the affected cortex. Thus it is quite obvious that the present case has nothing in common with the well-defined anatomical picture of Pick's disease.

As to the question of "premature ageing," one cannot deny that the diffuse pathological changes of the cortex and white matter, viz. lipoid degeneration, cortical and subcortical gliosis, and the atrophy of the inferior olives, are such as might be found in any senile brain. On the other hand, all localized parenchymatous system atrophies occurring in adult life, such as certain cerebellar atrophies and Huntington's chorea, are usually accompanied by the same kind of diffuse cortical and subcortical changes. This fact is important when we consider the pathology of the present case, because the cortical and subcortical changes, even in the areas of most marked degree, are certainly not sufficient to explain the thalamic degeneration as a retrograde one. In adult or senile brains much more severe atrophy of the cortex or gliosis of the white matter may occur without considerable thalamic changes. Even in Pick's circumscribed cortical atrophy any minor changes in the basal ganglia, which may be found, are, strangely enough, confined to the extrapyramidal system. Only in one case (Grünthal, 1936) were thalamic changes found, but these were apparently confined to postero-medial areas, and, judging from the photomicrograph, appear as marked subependymal gliosis rather than as true degeneration.

The somewhat symmetrical atrophy of the inferior olives belongs apparently to the same category of lesions as the diffuse subcortical and cortical changes. von Braunmühl (1928) has demonstrated how often, for some unknown reason, such bilateral "sector" atrophies occur in any sort of cerebral disease. The integrity of the cerebellum in the present case excludes the possibility of a retrograde degeneration. The so-called "thalamo-olivary tract," the origin of which in the thalamus is still doubtful, was preserved at the level of the medulla. Therefore the atrophy of the inferior olives cannot be due to transneuronal degeneration.

From these facts it appears, by the exclusion of all other possibilities,

that this is a genuine case of a system degeneration in the thalamus. There is, moreover, positive evidence for this assumption as there are here features typical of all parenchymatous system degenerations, e.g. those of the cerebellum or the lenticular nucleus. These features are: (1) the apparent symmetry of the process; (2) the "simple atrophy," i.e. the fact that the fatty products of degeneration are remarkably scarce compared with the extension and degree of degeneration; (3) the fact that the unaffected parts represent a developmental entity. The last-mentioned point is of the greatest theoretical interest and therefore needs special attention. Huber and Crosby (1929) have shown that the ventral nucleus and the geniculate bodies originate from a common matrix which is phylogenetically the oldest thalamic structure. The mid-line nuclei are very largely developed in lower mammals, and become inconspicuous in primates. These are just the formations which are bilaterally preserved in the present case. According to Edinger's well-known theory, in all the system degenerations which are due to what he called "abiotrophy," the process affects the more recent structures first or exclusively. This theory has been applied, sometimes with insufficient evidence, to the pathology of cerebellar atrophies, of Pick's disease (Onari and Spatz, 1926), of Huntington's chorea, and of various other conditions. Edinger's theory is particularly significant in the present case. Although care is necessary in making deductions from a single case unsupported as yet by analogies in the literature, the phylogenetic facts mentioned above bring more evidence for the assumption that here we have a genuine system degeneration.

There is some pathological evidence that other degenerations of this type, particularly the genuine cerebellar atrophies, be brought on by extraneous causes, such as chronic alcoholism (Jakob, 1912), malignant tumours (Greenfield, 1934), intestinal intoxication (Rossi, 1907), and may be associated with system degenerations. As it was impossible to carry out a complete post-mortem examination in the present case this question must be left open. However, the frequency of such toxic conditions and the great rarity of the associated degenerations in the central nervous system indicate that there must be, in certain individuals, a pre-existent constitutional factor—an "endogenous" vulnerability of the affected systems (Scherer, 1933).

It is not possible to bring the present case into relation with any previously defined pathological picture. The widespread disease of the basal ganglia and cortex first described by Jakob (1921) and usually quoted in the literature as "Jakob-Creutzfeld's disease" leads to considerable areas of gliosis in the thalamus, mainly its medial nuclei. There, however,

the thalamic changes are only part of a picture which is essentially that of a motor disease. This can best be understood from the term by which Jakob first described the condition, i.e. "spastic pseudosclerosis." It is characterized by a combined disease of the extrapyramidal and pyramidal system and the lower motor neuron. The degeneration of the cortex in area 6, of the striatum, and of the globus pallidus, are always most marked. All these features were completely absent in the present case, and, on the contrary, one of its most striking features was the contrast between the degenerated thalamus and the intact lenticular nucleus.

From this it is obvious that the present case cannot possibly be classified even as an "atypical" form of Jakob-Creutzfeld's or any other known disease. It is best described without attempt at classification as a case of bilateral symmetrical degeneration of the thalamus, excluding the ventral nuclei and geniculate bodies, and possibly including the "pretectal" area, rostral to the mid-brain. The last-mentioned area is not sufficiently defined in man; therefore it is possible that along with the medio-caudal periventricular parts, structures were involved which do not belong to the thalamus proper.

Clinico-Anatomical Aspect.

The most striking symptom in this case was the severe dementia which dominated the entire clinical picture. Common neurological experience shows that one has to be very careful in correlating disturbances of such complex functions as intelligence, attention and initiative, with lesions of any particular structure in the brain. It was, however, pointed out above that the fresh gliosis of the cortex and of the white matter are not sufficient to explain the mental disturbance; on the other hand, the destruction of large thalamic areas on both sides was so complete that one cannot avoid correlating this lesion with the clinical picture. Moreover, in contrast to neoplastic and inflammatory lesions, any general damage to the entire organ, e.g. from the mechanical or circulatory disturbance, can here be excluded with certainty. This makes the present case particularly valuable from the point of view of localization.

A previous investigation (Smyth and Stern, 1938) made it appear probable that the severe mental deterioration occurring in certain gliomas of the thalamus is related to the function of that structure, and has not only the significance of a general symptom of intracranial growth. Even gliomas which neither cause hydrocephalus nor invade adjoining structures to any considerable extent were shown to produce the picture of a severe dementia, especially if they occupied medial areas of both thalami.

It was then concluded that the deprivation of large cortical areas, especially the granular frontal cortex, from thalamic impulses might explain the dementia. It had to be admitted that the evidence obtained from the topographic study of tumours was not sufficiently conclusive. The present case, however, presents a pure degeneration of thalamic nuclei, and is therefore more appropriate for questions of localization.

A survey of the recent work on thalamo-cortical connections (Le Gros

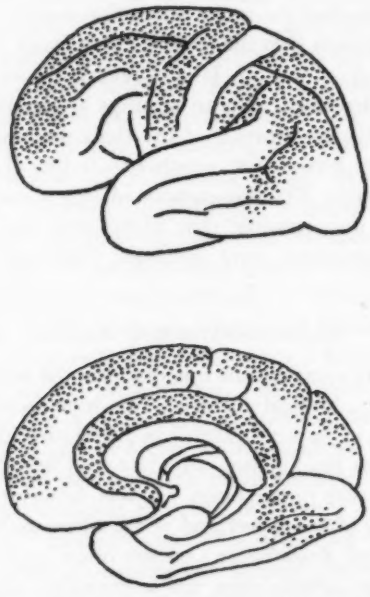

FIG. 6.—Indicates approximate extent of cortical areas which correspond to degenerated thalamic nuclei. This diagram is mainly based on recent investigations by W. E. Le Gros Clark and A. Earl Walker, quoted in text.

Clark, 1936, Earl Walker, 1938) shows that not only the sensory, auditory and visual cortical areas possess a thalamic representation ; large areas of phylogenetically recent origin and highly specialized function receive direct impulses from thalamic nuclei. The physiological and clinical significance of this fact is not yet fully recognized.

The present case demonstrates experimentally, as it were, the result of an isolation of vast areas of the cortex on both sides from thalamic impulses. Although the cyto-architecture of the human thalamus is somewhat different even from that of anthropoid apes one can apply the

results of the above-mentioned authors to the present case. Fig. 6 gives an approximate diagram of the cortical areas which correspond to the degenerated thalamic structures. The result of this isolation was clinically identical with that of a widespread severe affection of the cortex such as general paresis or Alzheimer's disease.

A feature which distinguishes this case from common cases of presenile dementia is the marked hypersomnia which was already present at an early stage. From the patient's history it appears to be not a mere result of inertia and lack of attention, but a sleep disturbance in the strict sense.

Bailey and Fulton (1929) have remarked that it is difficult to relate hypersomnia occurring in tumours of the infundibular region to any particular structure, because the mechanical effects of pressure cannot be entirely excluded. It is, however, certain that hypersomnia, though frequent with suprapituitary tumours, occurs much more frequently in gliomas which involve the walls of the 3rd ventricle (Cushing, 1932). Ranson, Kabat, and Magoun (1935) emphasized that they were never successful in producing sleep in animals by faradic stimulation of the hypothalamus; on the contrary, they always evoked a state of extreme emotional excitation. From this point of view it is noteworthy that all the hypothalamic nuclei were completely intact in the present case. This does not imply that the hypothalamus is not related to the function of sleep; in fact, some of the thalamic nuclei destroyed in this case represent intermediate neurons between the hypothalamus and the cortex. Thus, the anterior nuclei receive impulses from the mammillary bodies, and the dorso-medial nucleus which projects on to the granular frontal cortex apparently receives its impulses from the hypothalamus (Le Gros Clark, 1932). The marked somnolence, therefore, so frequently combined with diseases in the region of the 3rd ventricle may be due to a lesion of the second neuron of this hypothalamo-thalamo-cortical system. The present case demonstrates at any rate that a lesion of the hypothalamus itself is not necessary to produce this symptom. A further localization is not possible because of the extent of the lesion within the thalamus.

The same disadvantage exists as far as the iridoplegia is concerned. According to Hare, Magoun, and Ranson (1935) the pretectal area, i.e. the grey formations near the ventricle immediately rostral to the superior colliculi, contains the synapses for the light reflex. These areas appear to be affected in the present case, although, as shown above, their definition is not ascertained in man. Apart from this there was a certain amount of gliosis, without any damage to nerve cells in the superior colliculi. Exact localization, therefore, of the iridoplegia in the supranuclear apparatus is

not possible. It appears, however, that the present case contradicts the widely-held view that abolition of the reflex to both light and convergence is only found in disease of the peripheral neuron, for the nuclei for the intrinsic and extrinsic muscles of the eye were completely intact.

The ventral nuclei of the thalamus, which are, according to all recent anatomical reports, the only termination of secondary sensory neurons, were, except for the geniculate bodies and the mid-line nuclei, the only preserved structures of the thalamus proper. It would therefore have been of the greatest interest to obtain a picture of the sensory functions in the present case. This, however, was impossible owing to the patient's mental deterioration and complete lack of co-operation.

As far as the forced grasping and "tonic innervation" (Walshe and Robertson, 1933) are concerned, the case is of particular interest because the premotor area was intact on both sides, and the cortical changes as a whole were not sufficiently marked to account for these phenomena. This conforms with Kleist's (1927) observation that "tonic innervation" and forced grasping occur in association with thalamic lesions. It shows at any rate that these phenomena may occur when the major part of the thalamus is degenerated. It remains to be determined what is the actual mechanism of their production in a case like that here presented. Further observations may indicate whether or not they may be due to "de-afferentation" of the premotor area by the destruction of the anterior part of the lateral thalamic nucleus.

SUMMARY.

A case of severe presenile dementia with rapid course, accompanied by such neurological signs as loss of the pupillary reflexes and forced sucking and grasping movements is reported. The anatomical basis of this process was a selective bilateral symmetrical degeneration of the thalamus with exclusion of the ventral nucleus, arcuate nucleus, the mid-line nuclei, and the lateral and medial geniculate bodies. From various histological and topographical features it could be concluded that this was a peculiar system disease which has not hitherto been described. The symptomatology of the case is discussed on the basis of recent discoveries in the field of thalamo-cortical relations.

The author wishes to express his grateful thanks to Dr. J. G. Greenfield and to Dr. F. M. R. Walshe for their help and criticism, and for permission to use the post-mortem and clinical notes.

PLATE VI.

FIG. 1.

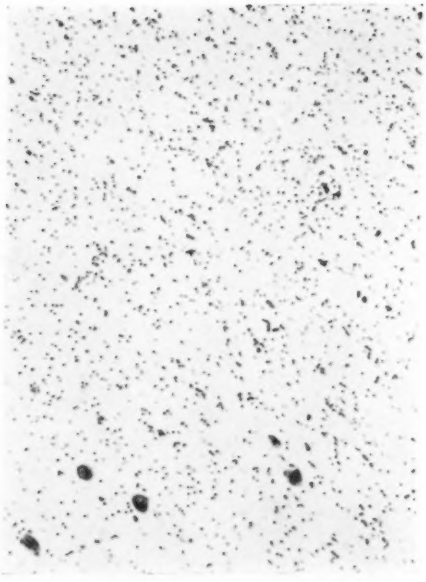

FIG. 3.

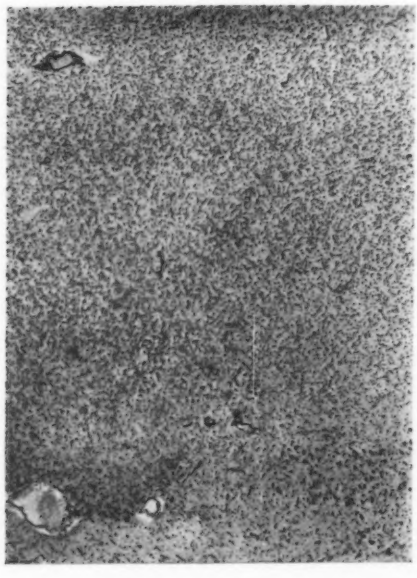

FIG. 4.

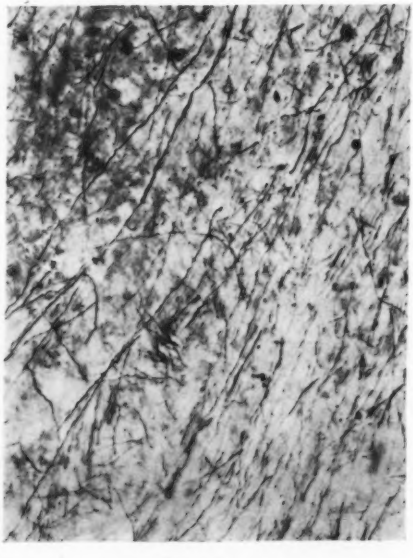

FIG. 5.

To illustrate article by K. Stern.

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LEGENDS FOR PLATE.

Fig. 1.—The pulvinar and its external medullary lamina are distinguished from the internal capsule (above the dotted line) only by the density of glia. No ganglion cells are preserved. The borderline between pulvinar and internal capsule is sharp (dotted line). (Nissl.)

Fig. 3.—Borderline between ventral and medial nucleus on left side. The ganglion cells of the ventral nucleus (lower part of picture) are well preserved. Remaining part of picture shows a diffuse gliosis. (Nissl.)

Fig. 4.—Dense even gliosis without any ganglion cells in dorso-medial area of right thalamus. The cluster of preserved ganglion cells in lower right corner belongs to mid-line nuclei. (Nissl.)

Fig. 5.—Bielschowsky-Gros picture from medial area in left thalamus which in cell-stains shows a dense gliosis and complete absence of ganglion cells. Loose bundles of fine neurofibrils (probably from afferent neurons) are preserved.

NEUROGENIC HYPERTHERMIA.[1]

(A Clinical Syndrome and Its Treatment.)

BY THEODORE C. ERICKSON.
(*Montreal.*)

The term neurogenic hyperthermia is often used indiscriminately when there is disease of the central nervous system associated with an elevated temperature. For this reason it is desirable to clarify the syndrome of neurogenic hyperthermia and to answer certain questions. If there be such an entity as neurogenic hyperthermia what are its anatomical and physiological substrata, what are its clinical features, and what is its treatment ?

Descriptions of hyperthermia following brain operations have been given by Kornblum (1925), Cushing (1932), and Gagel (1936). Since the only criterion which these discussions have in common is the fact that the patient had a high temperature, we will give a clinical delineation of the cases of hyperthermia considered to be neurogenic, followed by illustrative cases, a pathological and physiological analysis and a discussion of differential diagnosis and treatment. This clinical study was carried out from 1933 to 1938.

Clinical Picture.

The clinical picture is dramatic. Most striking is the rapid rise of rectal temperature, the relative warmth of the trunk and the icy dryness of the extremities. Venous blotching often appears in non-dependent portions of the skin of the extremities and less frequently in the trunk. Pilo-erection may be present and there is complete absence of sweating (anhydrosis). Thus it is evident that heat loss is reduced to a minimum as there is no sweating, and blood flow in the skin of the extremities is greatly reduced. The patient is quiet, practically never agitated, and almost always unconscious.

Hyperpnoea is usually but not invariably an accompaniment of the hyperthermia, the respiratory rate often rising as high as 40 or 50 per minute. Sometimes there are bouts of hyperpnoea (see case 2). Tachycardia is one of the earliest characteristic signs, often occurring before the rise of temperature. A heart rate of 140 per minute is usual and in the

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more severe cases it rises to 180 and above. The blood pressure is often very low but may be normal. As has been pointed out by Penfield (1936) "the heart seems to be driven at such a terrific rate that in about thirty-six hours, as a rule, the patient dies of heart failure." Often the hyperthermia can be controlled while the tachycardia cannot. The electrocardiogram may show many extrasystoles; this suggests stimulation of the posterior part of the hypothalamus (Beattie, Brow and Long, 1930).

Decerebrate rigidity may be associated with the hyperthermia due to extension of the disturbance into the mid-brain. Neurogenic gastroduodenal ulcers occasionally occur. However, the most constant parts of the syndrome are the hyperthermia, hyperpnoea and tachycardia which suggests that their respective centres in the brain are partially co-extensive or adjacent to one another.

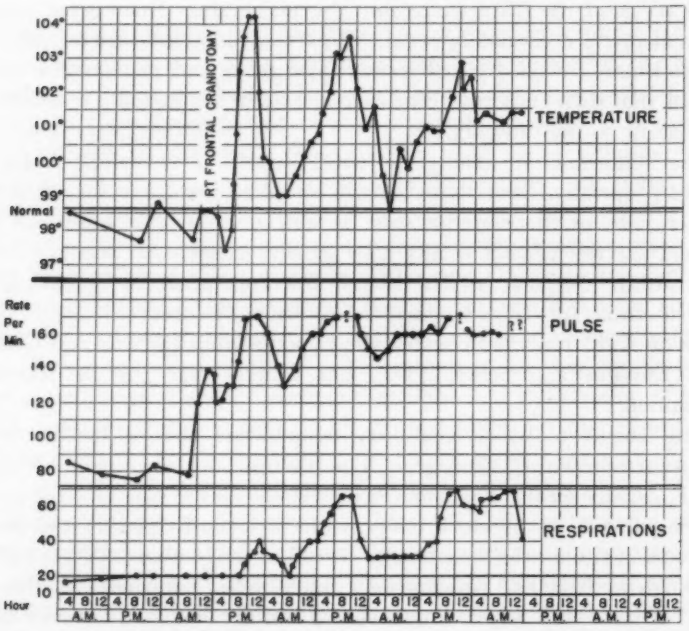
The syndrome of neurogenic hyperthermia is frequently observed following operative procedures on the pituitary fossa, the region of the 3rd ventricle, or the posterior fossa as well as after head injuries. The temperature rise usually occurs after general anæsthesia wears off or at least within the first twelve hours after operation or head injury. Hyperthermia (or hypothermia) is occasionally observed apart from operation with tumours involving the hypothalamus (Strauss and Globus, 1930, Davison and Selby, 1935, and others), but this is relatively uncommon.

The height to which the body temperature rises is not the most important criterion of neurogenic hyperthermia, for a temperature above 105° F. usually means inadequate watchfulness on the part of those caring for the patient. If the rectal temperature be taken frequently and proper measures instituted the temperature should never go above 104° or 105° F. Although we have had patients with much higher temperatures, those we shall cite have been watched more closely and the diagnosis has been based on a concatenation of hyperthermia, tachycardia, hyperpnoea and icy dry skin rather than on a rise of temperature above some arbitrarily fixed level such as 105° F.

The following cases show some of the variants of the typical clinical picture.

Case 1.—Craniopharyngeal epithelioma, removal, post-operative hyperthermia. S. E., female, aged 16, was admitted to the Montreal Neurological Institute, February 7, 1938, with a history of right temporal and occipital headache accompanied by nausea and vomiting of two months' duration, and failing vision of the right eye for one month. On February 11, 1938, a right frontal osteoplastic craniotomy was done by Dr. Penfield. After section of the right optic nerve the tumour, which was solid, was completely removed.

On the operating table (avertin, ether anesthesia) the patient's rectal temperature varied only from 98·2° to 98·6° F. The respirations varied between 20 and 30, the pulse between 100 and 120, the systolic blood-pressure from 120 to 140 and the diastolic from 60 to 70. Within an hour following operation the temperature fell to 97·2°, blood-pressure 102/50, pulse 120, respirations 26. Four hours after operation the temperature had risen to 104·2° with blood-pressure of 88/64 and imperceptible pulse (see chart). The extremities were icy cold and dry and venous mottling appeared in the extremities and spread to the trunk. The fluid intake was adequate and the cerebrospinal fluid pressure and cytology were within normal



Clinical Chart Case 1.—Craniopharyngeal epithelioma, removal, post-operative hyperthermia.

limits. Morphine sulphate in small doses (grains 1/32) was given and resulted in an evanescent improvement. Two transfusions of 500 c.c. of citrated blood produced a temporary improvement. It was found relatively easy to lower the body temperature by physical measures adjusting the environmental temperature. The cardiac system at first responded well to this lowering of body temperature but later it did not and measures were directed toward slowing the heart, perniciously accelerated by the hypothalamic derangement. Quinidine sulphate was given. Novocain and nupercaine were injected into the stellate ganglia by Dr. Cone in the attempt to block off cardiac stimulatory fibres. Therapy was of no avail, however, and the patient died seventy-two hours after operation.

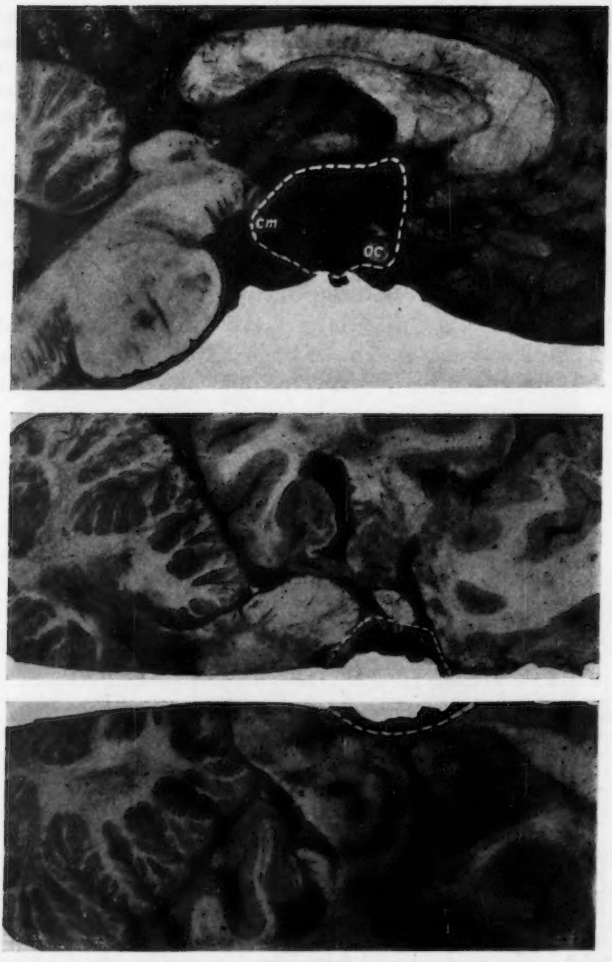
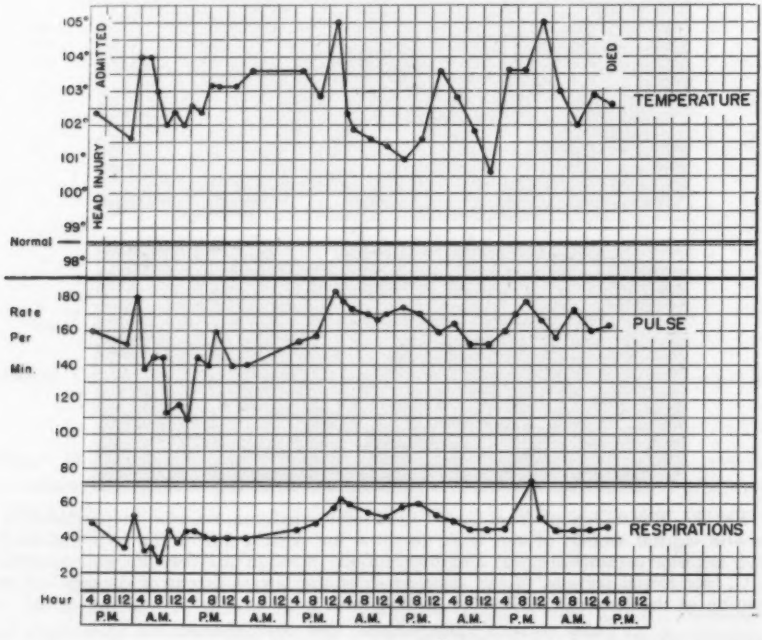


FIG. 1.—Brain sections from Case 1 (craniopharyngioma, removal, hyperthermia). A, Mid-sagittal section of the brain to show the destruction of the hypothalamus from anterior commissure and chiasma caudally through the corpora mammillaria. B, C, Horizontal sections of the same to show the lateral extent of damage. The location of the lesion is outlined in dotted lines.

c.m. corpora mammillaria. o.c. optic chiasm.

Examination of the head only was allowed. The operative site was clean and free from hæmorrhage or infection. The tuber cinereum was completely destroyed (fig. 1) and there was just a hæmorrhagic remnant of the corpora mammillare on either side. The anterior commissure could not be identified with certainty. The right optic nerve was destroyed and the chiasm distorted. There was no clot in the ventricles which were not enlarged. The tumour had been completely removed. Aside from the local destruction of the hypothalamus there were no other abnormalities in the brain except for a greyish area of softening in the dentate nucleus on the left.

Comment.—Except that alert nursing care prevented a high rise of temperature the above case illustrates well the cardinal features of neurogenic hyperthermia. The fact that the temperature fell below normal at first suggests that the mechanism of heat production was impaired as well as that of heat elimination, as will be discussed later. The tremendous acceleration of heart rate and the vascular changes responded only temporarily to blood transfusion, which helps to distinguish this from a case in which there has been much blood loss and the problem is merely one of restoring blood volume.



Clinical Chart Case 2.—Head injury, hyperthermia, paroxysms of hyperpnoea, focal hæmorrhages in the hypothalamus.

Case 2.—Head injury, hyperthermia, focal hæmorrhages in hypothalamus. H. A., aged 23, was admitted to the Royal Victoria Hospital, September 15, 1933, shortly after being hit by a car. He was unconscious with a fixed dilated pupil on the left and accentuated tonus and deep reflexes on the right. Paroxysmal attacks of hyperpnœa occurred shortly after admission with respirations increasing gradually to 48 and pulse to 160 but regular. With each paroxysm the face and

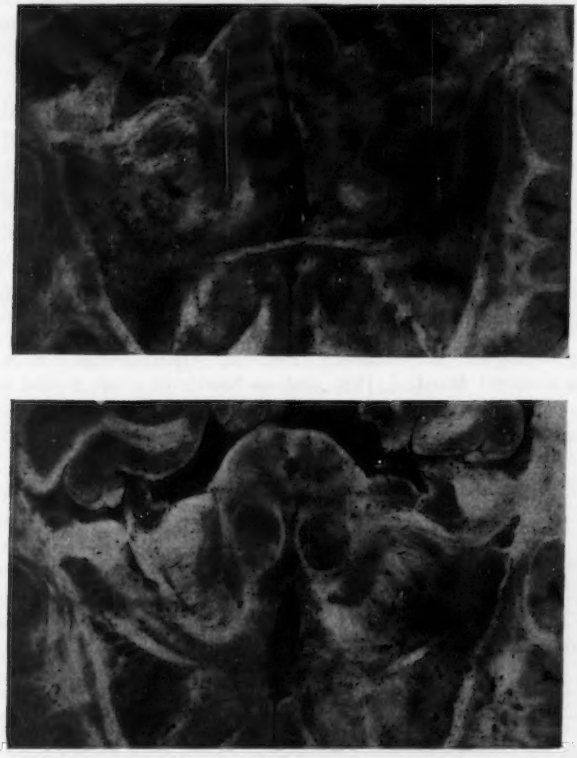


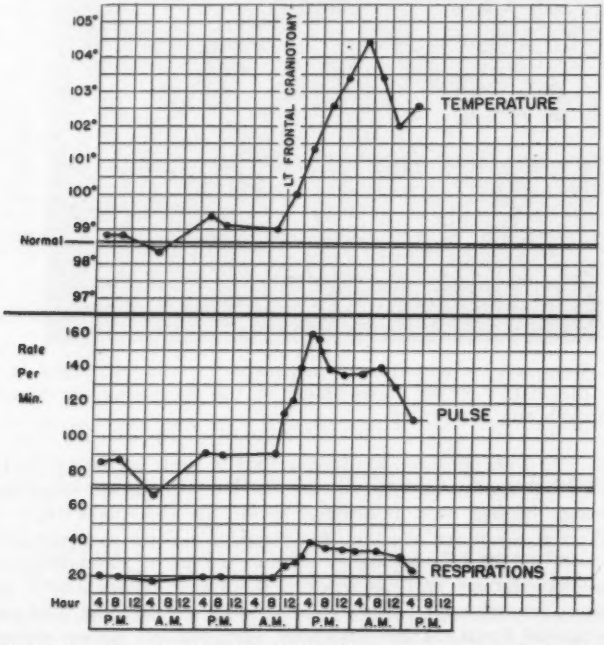
FIG. 2.—Horizontal sections through hypothalamus and mid-brain of Case 2. This shows the extent of the hæmorrhage in the hypothalamus in a case of hyperthermia following head injury.

neck were covered with perspiration that collected in pools in the eye sockets and neck, but from the nipples down he was dry and hot. There was shivering of the whole body and the legs were in extensor spasm, the right more rigid that the left. The left arm was flexed and the right extended. These paroxysms of hyperpnœa, etc., were set off by any slight stimulus just as in strychnine poisoning. Morphine sulphate (grains 1/32) in repeated doses and sodium amytol produced slight temporary improvement. Blood chlorides, CO_2 capacity and total protein N were within normal limits. Three days after admission the patient showed signs

of pulmonary consolidation and he died five days after the injury. The summary of the post-mortem findings was as follows: diffuse bronchopneumonia of the base of the left lung, diffuse punctate hæmorrhages of the cerebrum, pons and medulla, cortical adenoma of the adrenal, focal fibrosis and calcification of the spleen, and a recent lacerating wound of the scalp. On cutting the brain, discrete areas of hæmorrhage were observed in the corpus callosum, the fornix, the hypothalamus and the mid-brain (fig. 2). All except the tuber group of nuclei were involved on one side for the hæmorrhage extended obliquely to the section. Posteriorly it extended between the nuclei rubra to within 6 mm. of the aqueduct.

Comment.—Obviously the bronchopneumonia was terminal and did not account for the initial high temperature which was undoubtedly neurogenic in origin. The paroxysmal discharges were evidently due to irritation of centres for sweating, respiration, heart beat, standing rigidity and shivering. This presents a far more complex physiological picture than the usual case of the kind. It serves, however, to emphasize the fact that body temperature is intimately related to various organic processes and is the algebraic sum of these various functions which are each under the control of hypothalamic centres.

Case 3.—Meningeal fibroblastoma, removal, hyperthermia. B. A., female. aged 32, was admitted March 7, 1930, and on March 18 a left frontal osteoplastic

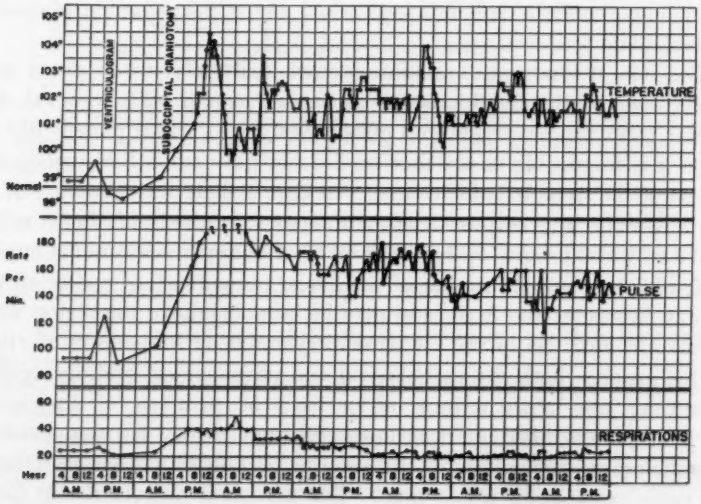


Clinical Chart Case 3.—Meningeal fibroblastoma, removal, hyperthermia.

craniotomy was performed. The tumour, a meningeal fibroblastoma arising from the olfactory groove, was completely removed by Dr. Penfield. As the wound was being closed the respiratory rate rose to 40 per minute and the pulse to 140. The rectal temperature rose rapidly to 104·4°. She failed to regain consciousness and died 24 hours after operation. Post-mortem examination showed definite congestion of the head of the caudate nucleus and anterior half of the putamen on the left side; the area supplied by the artery of Heubner. No gross abnormality was seen in the hypothalamus or elsewhere in the brain. The lesion in the corpus striatum appeared to be due to thrombosis of the anterior cerebral artery, or its branch, the artery of Heubner, perhaps secondary to retraction or to the use of the electrocautery.

Comment.—In this clinical case the hyperthermia resembles the "heat punctures" of Aronsohn and Sachs (1885), Wood (1880), Ott (1884), and others, because of the situation of the pathological lesion. Aronsohn and Sachs observed a rise of temperature within two to four hours after a lesion involving the head of the corpus striatum and the basis cranii (rabbits and dogs). In none of our other clinical cases has the pathological lesion involved the region of the head of the corpus striatum.

Case 4.—Glioma arising from quadrigeminal plate, removal, hyperthermia, recovery. I. B., male, aged 9, was operated on January 25, 1934. Through a suboccipital craniotomy Dr. Cone removed a glioma (unclassified) from the roof of the fourth ventricle and mid-brain. Immediately the extremities became cold and



Clinical Chart Case 4.—Glioma arising from the quadrigeminal plate, removal, hyperthermia, recovery.

dry, the temperature rose to 104·6°, the respiratory rate varied between 40 and 50 per minute and the pulse was over 150 with much irregularity (extrasystoles). Removal of bed clothes, alcohol sponges, the use of an electric fan, and repeated doses of aspirin and morphine caused an improvement and the patient finally left the hospital March 2, 1934. He was still living and well in August, 1938. Chart 4 shows the typical clinical chart during the immediate post-operative period.

Comment.—The operative approach was so strictly localized in the posterior fossa that no other mechanism for the hyperthermia can be suggested in this case than a lesion of ascending or descending thermotaxic fibres in the mid-brain or medulla. Although the tumour was limited to the corpora quadrigemina the operative approach may have produced œdema ventral to the aqueduct of Sylvius as well.

Pathological Analysis.

Twenty autopsy specimens from patients with neurogenic hyperthermia were studied. In sixteen of these there were definite gross lesions in the hypothalamus or in the brain-stem where they could involve experimentally demonstrated heat-regulatory centres or pathways. The extent and distribution of some of these lesions is shown in fig. 3. The hypothalamus was directly involved in seven instances. Fig. 3 emphasizes the distribution of cases and not the concentration, i.e. two out of seven lesions in the hypothalamus are indicated while the one lesion in the quadrigeminal plate is shown.

The typical syndrome sometimes occurs in the absence of direct gross involvement of the hypothalamus as in the patient with removal of a tumour from the quadrigeminal plate (see Case 4). This patient did not die so it is impossible to say that he did not have small hæmorrhages or œdema of the hypothalamic centres. In Case 3 there was softening of the cranial part of the corpus striatum due to thrombosis of the artery of Heubner without any evident lesion in the hypothalamus. The area involved is comparable to that of the "heat punctures" of earlier authors such as Aronsohn and Sachs and may be homologous to the region which is active in heat loss in the cat, as demonstrated by Magoun *et al.* (1938). In this instance both the pathological and physiological findings agree in explaining the hyperthermias on a basis of paralysis of the central mechanism concerned in heat loss. With extensive destruction of the hypothalamus, particularly of the anterior portion as in Case 1 (cf. fig. 1), the same explanation would hold. The persistent tachycardia in Case 1 is apparently related to a release of cardiac acceleratory centres in the posterior part of the hypothalamus.

The scattered focal hæmorrhages in the hypothalamus which were found in Case 2 (cf. fig. 2) are especially interesting in view of the atypical accompaniments of the hyperthermia. Anhydrosis and icy dry skin were observed only below the nipples while above there was profuse perspiration. This suggests that there had been a selective paralysis of some heat-loss mechanisms with stimulation of others. In the same way may be explained the bouts of hyperpnoea which some patients have at intervals.

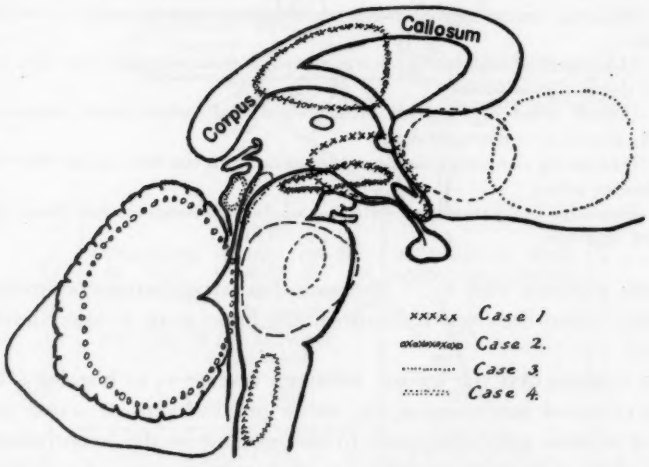


FIG. 3.—Diagram of the brain-stem to show distribution of some of the pathological lesions in cases of hyperthermia. The scatter confirms the conception that the reflex arcs concerned in temperature regulation are widely spread in the brain-stem.

Pathological material from the following cases has been studied as well as from those cases which have been discussed in detail previously.

S. G.—Perineurial fibroblastoma of right 12th cranial nerve with hæmorrhages in the medulla.

C.—Perineurial fibroblastoma of the 8th cranial nerve ; petechial hæmorrhages on the left side of the pons.

M. H.—Cyst of medulla ; cystic arachnoiditis in posterior fossa, sagittal sinus thrombosis.

M. W.—Massive tumour (astroblastoma) involving both frontal lobes and extending back to the mid-brain.

C. W.—Cerebral concussion, contusion and laceration ; one area of hæmorrhage in posterior part of third ventricle.

R. H.—Astroblastoma of optic chiasma extending through the hypothalamus to the pons.

J. S.—Diffuse brain injury—third ventricle grossly normal but slight congestion of left putamen.

M. D.—Medulloblastoma—right cerebellar hemisphere.

E. Q.—Hæmorrhage in the temporal lobe—third ventricle normal.

H. T.—Head injury—third ventricle and basal ganglia normal.

B. O.—Cerebral concussion and subarachnoid hæmorrhage, punctate hæmorrhages in wall of third ventricle extending from the lamina terminalis three-quarters of the way back to the corpora mammillaria.

F. O.—Midline cerebellar hæmangioma—hæmorrhage around the aqueduct of Sylvius.

Th.—Bilateral frontal astroblastoma—hæmorrhage just anterior to the lamina terminalis.

Ca.—Meningeal fibroblastoma of right middle fossa extending to the midline and into the posterior fossa.

Fe.—Diffuse brain injury with intracerebral and subarachnoid hæmorrhages but no localization in diencephalon.

Bo.—Infiltrating tumour of the pons extending from the floor of the 4th ventricle to the basilar artery.

Pa.—Extensive infiltration and softening of the left temporal lobe, basal ganglia and third ventricle.

These, together with fig. 3, illustrate that hyperthermia occurred most frequently when the hypothalamus or the brain stem at lower levels was involved.

It is evident that the lesions, although diverse as to histology, have a certain common denominator, i.e. either proximity to or actual involvement of regions most concerned in thermotaxis in the hypothalamus or their pathways in more caudal parts of the brain stem. A consideration of experimental physiological studies is necessary for further interpretation.

Physiological Analysis.

Body temperature is the product of several physiological processes (fig. 4) which may be grouped into those concerned with heat production (chemical regulation) and those concerned with heat elimination (physical regulation). Eighty per cent. or more of body heat is produced in the muscles (and glands). Since the greater part of heat production occurs in the deeper parts of the body the first stage in heat elimination is shift of heat to the surface where it may be lost (indicated in fig. 4 by dotted lines) (for our present purposes we may ignore the quantitatively insignificant rôle of the excreta and respiration in heat loss in man). This is accomplished in two ways, first by direct conduction of heat through the tissues, and second by internal convection of heat by means of the blood stream. Convection of heat by the circulating blood is used in a sense analogous

to convection of heat in a liquid or air, i.e. transference of heat from place to place by actual motions of the hot body. When the heat finally has reached the skin its loss becomes a purely physical process (Burton, 1934)

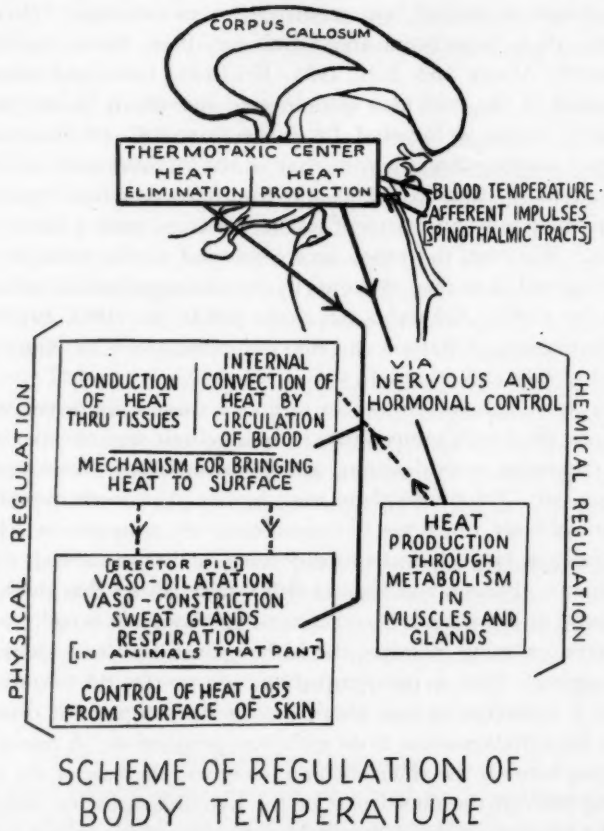


FIG. 4.—Scheme of regulation of body temperature. Dotted lines indicate the course of heat flow in the body while solid lines indicate the nervous factors in thermotaxis. Upward arrows indicate stimulating factors of hypothalamic centres and downward arrows projection fibres to lower centres.

controlled by sweating and vasomotor changes. Apart from pointing out the prominent part played by the vasomotor responses in the amount of heat loss from the skin, further consideration of the peripheral mechanism in heat regulation is beyond the scope of this paper. The reader is

referred to the reviews of Barbour (1921), Isenschmid (1926), Bazett (1927), and Deighton (1933), as well as to the excellent paper of Burton.

A well established fact is that in the hypothalamus, at the level of the mammillary bodies, there is a region the preservation of which is essential to maintenance of normal heat regulation or thermotaxis.[1] (Isenschmid and Krehl, 1912, Isenschmid and Schnitzler, 1914, Bazett and Penfield, 1922, Bazett, Alpers and Erb, 1933, Erickson, 1934, and others.) A decerebration at the collicular level in cats and which passes below this thermotaxic centre is followed by a condition of poikilothermia, the temperature varying directly with that of the environment as with cold-blooded animals. Ranson (1935) and his co-workers have localized the region more laterally by means of lesions produced with a Horsley-Clarke apparatus. However, the reflex arcs concerned in thermotaxis must be more widespread than this, as shown by the old experiments on heat puncture: Richet (1885), Aronsohn and Sachs (1885), Ott (1884, 1914) and the newer observations of Ranson and his co-workers (1937), of Pinkston, Bard and Rioch (1934), and others.

A priori, we should not expect to find a sharply localized centre for thermotaxis since body temperature is the algebraic sum of other variables, such as cutaneous vasodilatation, general metabolism, water-metabolism, respiration, etc. Of course there may be one thermostat presiding over these various body functions as they affect body temperature. However, all the evidence, both clinical and experimental, is against such a precisely localized area. Ranson and Ingram (1935) have shown that the heat regulating centre in the posterior part of the hypothalamus is really concerned in heat production, in guarding the body against heat loss. Some authors have suggested that a parasympathetic centre in the anterior hypothalamus is concerned in heat elimination and a sympathetic centre in the posterior hypothalamus has to do with heat production. A centre for heat elimination between the anterior commissure and the base of the brain and extending back in the dorsal part of the hypothalamus has been demonstrated by Magoun *et al.* (1938). By local heating of the animal brain, with low voltage, high-frequency currents passed between electrodes oriented by the Horsley-Clarke apparatus, they obtained acceleration of respiratory rate, panting, and sweating of the foot pads.

Normally stimulation of these thermotaxic centres may be produced, either by changes in blood temperature or by afferent nervous impulses

[1] Thermotaxis is used to designate the mechanisms concerned in the adjustment of body temperature in preference to that word of dual etymological derivation, " thermoregulation."

(anterolateral column, spinothalamic tracts), Greving (1931), Pickering (1931), Jung, Doupe and Carmichael (1937). Isenschmid and Schnitzler (1914) stated that efferent thermotaxic fibres are widely scattered in the ventral portion of the brain-stem. Foerster (1936) stated that in the cervical cord these fibres are localized in the anterolateral portion, basing this opinion on the occurrence of hyperthermia following section of the spino-thalamic tracts.

Neurogenic hyperthermia cannot be said to have been reproduced experimentally, for "heat puncture" is only a fragment of the whole picture (Erickson, 1934). The slight hyperthermia following a lesion in the anterior hypothalamus of animals (Teague and Ranson, 1936) is due to lack of panting when exposed to high environmental temperatures. At best a composite picture may be constructed from the results of different experiments on the hypothalamus. This difference between man and the lower animals: that is, in the appearance of neurogenic hyperthermia, may be explained by quantitative differences in the manner of heat loss. In man heat loss occurs mainly by way of the skin, but in the usual laboratory animals the respiratory tract plays a much larger part. Theoretically hyperthermia may be due to decreased heat elimination, increased heat production or a combination of the two as a result of a lesion affecting such centres. From the clinical picture, neurogenic hyperthermia seems to be due largely to a decrease of heat loss.

In those instances in which no gross lesion was demonstrable in the hypothalamus there may have been circulatory alteration in the hypothalamus. An inadequate circulation in the hypothalamus might, by local lowering of temperature, induce a vicious cycle because of lack of stimulation of a heat loss centre. The work of Barbour and of Magoun *et al.* furnish an experimental basis for such an explanation.

Differential Diagnosis.

Neurogenic hyperthermia may be simulated by hyperthermia due to many other causes which may be classified as follows:—

A Clinical Classification of Hyperthermia.

I. Hyperthermia due to Infection.

II. Hyperthermia due to Failure of Heat Elimination (not neurogenic) particularly internal convection.

- (*a*) Inadequate circulation.
- (*b*) Anhydremia. This may be produced by:—
  - (1) Excessive hypertonic injections.
  - (2) Low fluid intake.

III. Neurogenic Hyperthermia (in broadest sense but disregarding drugs and toxins which act on hypothalamic centres).
  (*a*) Spinal Poikilothermia (Hyperthermia or hypothermia).
  (*b*) Central Poikilothermia due to Inhibition or Paralysis of Thermotaxic centres.
    (1) Anæsthesia.
    (2) Acutely increased intracranial pressure.
  (*c*) Neurogenic (Central or hypothalamic) Hyperthermia.

Even the elevated temperature of infections may be due to the effect of toxins on the hypothalamic centres (Citron and Leschke, 1913) and so be fundamentally neurogenic in origin. In the mind of the general surgeon elevated temperature is almost synonymous with infection and rightly so. The same should be true in dealing with the nervous system, but other causes must more often be considered. If the temperature rises shortly after a brain operation or injury neurogenic hyperthermia must be considered for the temperature elevation of infection occurs only two or three days later.

The circulation of blood plays a part in heat elimination by acting as an agent for the internal convection of heat, i.e. transporting the heat from the locus of production to the surface where it can be eliminated by radiation or evaporation. A poor circulation of blood may decrease metabolism and thus decrease heat production, leading one to expect a lowering of body temperature, but the interference with heat elimination by curtailment of internal convection is quantitatively greater than any effect on heat production. It has been shown that the mechanisms operative in chronic cardiac failure may produce a fever (Cohn and Steele, 1934). Acute circulatory insufficiency may produce a rise of temperature in the same way by inadequate internal convection of heat and by concomitant cutaneous vasoconstriction. It is an old saying that people with poor circulation have cold hands and cold feet and the same holds true for patients with neurogenic hyperthermia.

Anhydræmia such as produced by a combination of low fluid intake and injection of excessive hypertonic solutions may lead to an elevated temperature as was demonstrated experimentally by the work of Balcar, Sansum and Woodyatt (1919). In neurosurgical cases where hypertonic solutions are commonly used to reduce increased intracranial pressure this may occasionally contribute to a rise of temperature.

A normal man maintains his body at a more constant temperature than any of the lower animals. He is a more perfect homotherm than any of

the animals studied in the laboratory but even he may, under certain abnormal conditions, become poikilothermic with a body temperature which varies directly with that of the environment. This effect may be partial or complete. The poikilothermia, which is caused by a lesion of the cervical or high thoracic region of the spinal cord (Gardiner and Pembrey, 1912), is usually manifest as a hyperthermia because most good hospitals protect their patients against heat loss all too well. However, from the same lesion under conditions of military surgery a low temperature may be the rule (Gordon Holmes, 1915).

In a series of 15 cats it was found that acutely increased intracranial pressure may cause a poikilothermia (unpublished experiments by the author). An increased or a decreased temperature resulted, depending upon the thermal environment in which the experiments were performed. Clinical confirmation of this effect of acute increase of intracranial pressure was furnished by study of a group of cases with hæmorrhage from the middle meningeal artery. On admission these cases showed either a high, a low, or a normal temperature depending upon the environmental temperature to which they had been exposed prior to admission. After being cared for in the hospital their temperatures were always high or normal, such as one would expect with inhibition of thermotaxic centres. Not infrequently such cases are complicated by the presence of intracerebral hæmorrhages involving the thermotaxic centres or pathways, thus producing a positive hyperthermia.

Any general anæsthetic, whether it be avertin, ether or the barbiturates causes a marked derangement of the thermo-taxic centres. The fact that patients, during and after general anæsthesia, are sensitive to cold has long been emphasized in the minds of the best nursing and resident staffs but the fact that they are just as susceptible to excessive heat is often not realized. It used to be a common occurrence several years ago, before the nursing staff was centralized and especially trained, to have the patient, upon leaving the operating room with a normal or slightly elevated temperature, put in a preheated bed with hot water bottles and three or four heavy blankets. These patients, from no other cause, would develop symptoms closely simulating neurogenic hyperthermia. If they had the pathological and physiological substrata of a neurogenic hyperthermia, coals were added to the fire.

What may be called the momentum of a rising body temperature may cause a very deceptive clinical appearance. This may be readily demonstrated in the laboratory. A cat which has been rendered poikilothermic by a low decerebration and which has a rising rectal temperature because

of a high environmental temperature continues to show a rise of temperature for a short interval of time after removal of the external heat. Similarly a patient with a rising temperature may show a continued rise of temperature for a short time after exposure to a cooler environment. This does not necessarily mean that there is an active or positive neurogenic hyperthermia. A rising temperature is part of a vicious cycle, increased body temperature increases metabolism by increasing the velocity of the chemical reactions and the increased heat thus produced raises, in turn, the temperature.

Treatment.

Once fully developed, neurogenic hyperthermia presents a serious outlook. Tepid sponges, ice-water enemas and ice-bags can be used if removal of covers from the patients and lowering of room temperature are not effective. In a true neurogenic hyperthermia local application of heat does not produce a vasodilatation of the cold dry extremities. By repeated small doses of morphine (grains 1/32 or 1/64) together with the usual physical measures for lowering temperature, some ground may be gained. This helps to quiet the hyperpnœa and tachycardia and tends to cause vasodilatation, rendering cooling applications to the skin more effective. Aspirin, though less effective, seems to be of use when given in large doses.

Other measures, some with effect, have been tried in isolated cases. Cushing reported that intraventricular pituitrin caused a fall of temperature in one case of neurogenic hyperthermia. Local application of carbon dioxide to the skin in a suitable form might be effective in dilating the skin vessels and promoting cooling (Bazett). Drugs such as physostigmin and acetyl B methyl choline (mecholyl) have been tried but are limited in use because of their effect on the blood-pressure. These patients are more sensitive than normal to mecholyl, which in itself is significant. Minute doses of mecholyl may, however, be of distinct use. Tachycardia is often one of the most prominent features and death is caused by a circulatory failure. Various measures have been used to slow the heart, such as quinidine and injection of the stellate ganglia, but without uniform success. Needless to say one should always be sure that the fluid intake is adequate. *Transfusion is often indicated and should be done in the early stages.*

It is to be emphasized that neurogenic hyperthermia, as well as other hyperthermias, may be prevented or at least alleviated *by close routine attention to the patient's rectal temperature in relation to his thermal environment.* This is necessary mainly in the immediate post-operative or post-traumatic period, when readings should be taken every half hour. Following operation on the hypophysis, the third ventricle, or the posterior

fossa even a small rise of temperature above 100° should be a signal for removing the bed coverings from the patient. If the rise continues in spite of this the room temperature should be lowered, air movement should be increased by use of a fan and if necessary alcohol sponges and ice water enemas, etc., should be instituted. Aspirin in large doses and morphine in small doses are then used.

To illustrate the effectiveness of these simple routine procedures, we may say that during the two years preceding July, 1934, before these measures were first instituted, there were at least 21 cases which were diagnosed as neurogenic hyperthermia. In the four years since these measures have been closely followed, there have been only five.

Summary and Conclusions.

The syndrome of neurogenic hyperthermia is discussed on the basis of observations of clinical cases, of studies on pathological specimens and on experimental work. The differential diagnosis and treatment are outlined.

From this study the following conclusions may be drawn.

(1) Neurogenic hyperthermia is manifested by a high internal temperature and icy cold dry skin occurring shortly after head injury or operation in the region of the 3rd ventricle or posterior fossa, and less frequently pre-operatively with tumours in the diencephalon. The patient is unconscious, the respiratory and pulse rates are usually very high and the outcome is often fatal.

(2) Body temperature is the algebraic sum of the functions of the heart and general circulation of blood, of the general metabolism, of the cutaneous vasoconstriction and vasodilatation, and of the rapidity of respiration. For this reason the manifestations of neurogenic hyperthermia may vary inasmuch as variable portions of the neuronal centres and pathways directly or indirectly concerned with heat regulation are affected by the lesion.

(3) Prophylactic measures are genuinely effective in lowering the incidence and mortality from neurogenic hyperthermia.

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THE SENSORY INNERVATION OF THE SPINAL ACCESSORY AND TONGUE MUSCULATURE IN THE RHESUS MONKEY.

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THE peripheral portion of the spinal accessory nerve in the cat carries proprioceptive fibres from the accessory muscles (sternomastoid, cleidomastoid and trapezius) (Corbin and Harrison, 1938; Echlin and Propper, 1938). By means of the cathode ray oscillograph and degeneration experiments, we have found that these proprioceptive fibres enter the central nervous system by way of the peripheral anastomoses of the upper five cervical ventral rami with the spinal accessory nerve, and therefore have their cells of origin in the respective dorsal root ganglia (Corbin and Harrison, 1938). Similar studies on the rabbit reveal that the 3rd and 4th cervical spinal nerves, joining the accessory nerve in the neck, carry the muscle sense fibres from the accessory muscles in this animal (Yee, Harrison and Corbin, 1939). In neither the cat nor the rabbit could action potentials indicative of proprioceptive activity be obtained in the portion of the spinal accessory nerve immediately external to the jugular foramen (therefore proximal to the anastomoses of the ventral rami with the accessory nerve) during stretch of the accessory musculature, although this stimulus regularly evoked such potentials in the more peripheral portions of the accessory nerve and various cervical ventral rami. Hence in these animals the intracranial and intraspinal portions of the spinal accessory nerve are primarily motor. While admitting that impulses arising in the more caudally situated accessory muscles (trapezii) in the cat probably pass centrally over the cervical ventral rami, Tsuruyama (1938) believes that proprioceptive impulses from the rostrally located muscles (sternomastoid and cleidomastoid) pass centrally with the accessory and "nach dem Eintritt ins Marks intramedullär zur hinteren Wurzel sich begeben, . . ." Certainly our experiments indicate little need for such an explanation.

In the cat and rabbit, faradic stimulation of the peripheral stumps of

the cut upper five cervical ventral rami never produced contraction of the accessory muscles. Accordingly in these animals it would appear that the accessory musculature receives its entire motor innervation through the spinal accessory nerve. Similarly in the following experiments we have found that the accessory musculature in the monkey receives its entire motor innervation through the spinal accessory nerve and its sensory supply from the dorsal root ganglia of C.2, C.3, and C.4, via the respective cervical ventral rami and their peripheral anastomoses with the accessory nerve.

Corbin, Lhamon and Petit (1937) found a small number (1 per cent. to 5 per cent.) of degenerating fibres in the most peripheral portion of the hypoglossal nerve after removal of C.2 dorsal root ganglion in the monkey. This suggested an extracranial contribution of sensory (probably proprioceptive) fibres to the tongue musculature from this ganglion. A similar contribution from C.1 dorsal root ganglion to the muscular portion of the hypoglossal nerve was found in the rabbit by Yee, Harrison and Corbin (1939).

Although Carleton (1938) found no muscle spindles in the rabbit tongue, she reported complete degeneration of interstitial and epilemmal terminals in the tongue following section of the hypoglossal nerve. Such terminals were present after section of the lingual nerve. Similar observations were made by Corbin and Yee (unpublished) on the cat and monkey tongue using a methylene blue technique. This is contrary to what one would expect from the work of Barron (1936) but agrees with our physiological results (1938) in which we found tactile but no proprioceptive impulses in the lingual nerve upon stretching or twisting the tongue. No evidence for a sensory contribution from the upper cervical dorsal root ganglia to the hypoglossal nerve was found in the cat (Hinsey and Corbin, 1934 ; Barron, 1936 ; Corbin and Harrison, 1938).

Material and Methods.

Fourteen adult Macacus rhesus monkeys were used in this study. All operative procedures were carried out under intravenous sodium pentobarbital anesthesia. Using the cathode ray oscillograph and loud speaker we traced action potentials, elicited through stretch of the accessory muscles, through various branches of the accessory nerve and the cervical ventral rami. Accessory muscles were isolated except for their nerve supply and rostral attachments. Recording leads consisted of two 26 gauge silver wires chlorided electrically and separated from 1 to 3 mm. Potentials were amplified by a three stage resistance coupled amplifier. An output of 10 u V. gave a deflection of 1 cm. on the screen at the highest amplification used. The usual precautions to avoid extraneous impulses were observed (Adrian, 1930). The peripheral stumps of the upper five cervical ventral rami were tested

with bipolar faradic stimulation in those animals which were used for oscillographic studies. Stimulation was through platinum electrodes with a tip separation of 2 mm.

Histological experiments in which the upper five cervical ventral rami were divided in various bilateral combinations were also carried out (See table). Following

TABLE SHOWING VARIOUS NERVES DIVIDED.

Monkey No.		801	802	803	804	805	806
Spinal nerve (Ventral ramus) divided	Left	C.3	C.4	C.2[1]	C.3	C.4	C.2[1]
	Right	C.2	C.4	C.3	C.2	C.2	C.2[1]

[1] Only the rostral branch of C.2 to the hypoglossus was divided.

adequate degeneration time, usually 7 days, the various nerves studied, including various portions of the twelfth cranial nerve, were removed and placed in 1 per cent. osmic acid for 24 hours. They then were carefully teased in glycerine and examined for degeneration. The direct osmic acid method has proved of much greater value to us for the study of degeneration in peripheral nerves than the Marchi method.

RESULTS AND DISCUSSION.

The anastomoses between the upper cervical ventral rami and the accessory nerve in the monkey have been described by Tanaka (1932), Christensen (1933) and Corbin, Lhamon and Petit (1936). The most frequent type of anastomosis is illustrated in the diagram in which we have also indicated the course of the sensory fibres to the accessory muscles.

Stretching of the inferior trapezius muscle regularly elicited proprioceptive action potentials (as defined by Matthews, 1933; and Corbin and Harrison, 1938) in that portion of C.4 ventral ramus which communicates with the accessory nerve, occasionally in C.3 ventral ramus. Impulses initiated through stretch of the superior trapezius passed centrally over branches of the ventral rami C.2, C.3 and C.4 which anastomose with the accessory nerve. Stretching of the sternocleidomastoid group uniformly elicited action potentials from C.2 and C.3 ventral rami, but never in C.4 ventral ramus.

When the peripheral end of the cut spinal accessory nerve (just external to the jugular foramen) was placed on recording leads, an increase in the amplitude and frequency of action potentials was noted on stretching the sternocleidomastoid muscle. This activity did not appear when the branch to this muscle from the accessory was cut. No such response was elicited by stretching the trapezii, although stretching the latter muscle evoked a

marked response in those portions of the accessory peripheral to the anastomotic branches of C.3 and C.4. Because the monkey's neck is short, the length of the accessory nerve between the jugular foramen and the sternomastoid muscle is less than in the cat and rabbit. It is therefore difficult to place this portion of the nerve on the leads without including those fibres from C.2 and C.3 which enter the branches to the sternomastoid and cleidomastoid muscles. We feel that this is probably the explanation for our obtaining responses from this portion of the accessory nerve in the monkey whereas the same portion of this nerve was silent in the cat and rabbit. In view of our results in the latter animals we believe it unlikely that any proprioceptive fibres from the sternomastoid muscle pass intracranially in the accessory nerve. However, the latter possibility certainly exists, and if so, such fibres may have their cells of origin in those small ganglia occasionally found along the course of the spinal accessory (Weigner, 1901 ; Streeter, 1905 ; Fahmy, 1927 ; Windle, 1931) or in the upper cervical dorsal root ganglia, to be reached by intraspinal anastomoses between the accessory and the dorsal roots (Kazzander, 1891 ; Weigner, 1901 ; Streeter, 1905 ; Pearson, 1937). We have been unable to find such anastomoses in our studies of the cord and accessory nerve in the monkey.

As in the cat and rabbit, stimulation of the peripheral ends of the cut cervical ventral rami of the monkey never caused contraction of the muscles innervated by the spinal accessory nerve. Strauss and Howell (1936) obtained "weak though definite action of the trapezius," in one chimpanzee from stimulation of the peripheral stump of a branch from C.3 and C.4 spinal nerves to the accessory. However, since we have never observed such contraction, we conclude that any degenerating fibres found in the accessory nerve following section of the ventral rami must be sensory in nature.

In all cases the medium—large-sized myelinated fibres were the type found to be degenerating. Section of C.2 ventral ramus led to degeneration of a large number of fibres in the accessory branches to the sternocleidomastoid muscles. A smaller number of fibres from C.2 continued in the accessory supplying the trapezius muscles. Section of C.3 ventral ramus resulted in degeneration of a large number of fibres in the branches to the sternocleidomastoid muscles and in the peripheral portion of the accessory and its branches to the trapezii. Following section of C.4 ventral ramus, degenerating fibres were followed peripherally in the accessory through its various branches to the trapezii but no degenerating fibres passed to the sternocleidomastoid muscles. The results of the oscillographic and degeneration experiments are summarized in the diagram,

in which it should be noted, that the anastomotic branches between the cervical ventral rami and the accessory nerve are entirely sensory. The results of the degeneration experiments are obviously in entire agreement with the oscillographic studies.

These findings agree with those obtained in the cat and rabbit ; that is, that the proprioceptive fibres to the accessory muscles arise in the upper cervical dorsal root ganglia (2, 3, and 4, in monkey) and pass peripherally over the respective spinal nerves to join the extracranial portion of the spinal accessory nerve before passing to the muscles. Furthermore, our stimulation experiments in the cat, rabbit and monkey show that the anastomotic branches of the upper cervical nerves with the spinal accessory are entirely sensory. In man, as in the monkey, there are extraspinal anastomoses between C.2, C.3, and C.4 and the accessory nerve and it would therefore appear to be a reasonable conclusion that these branches contain sensory fibres destined for the sternocleidomastoid and trapezius muscles.

In the monkey, C.2 ventral ramus gives off a small branch which passes rostrally with a similar branch from C.1 and joins the hypoglossal nerve. C.2 fibres may also pass with C.3 fibres directly to the hypoglossal nerve more peripherally or, as is more usual, anastomose with the ramus descendens to form the ansa hypoglossi. Section of the rostral branch from C.2 to the hypoglossal nerve results in degeneration of a bundle of medium-small sized myelinated fibres which pass peripherally with the hypoglossus to enter the descending ramus. However, a small number may be traced peripherally in the hypoglossus directly into the tongue musculature. These fibres form about 2 per cent. to 5 per cent. of the total myelinated variety in the peripheral portion of the hypoglossal nerve. Similarly, section of that portion of the ventral ramus of C.2 which joins with that of C.3 to form the ansa, also leads to a small amount of degeneration in the most distal portion of the hypoglossal nerve. This contribution is less in amount, however, than that which accompanies this nerve from the rostral branch of C.2. This agrees with our results on Rhesus monkeys in which the C.2 dorsal root ganglion was removed (Corbin, Lhamon and Petit, 1937), and indicates that the degenerating fibres found in the hypoglossal nerve after section of C.2 are probably sensory in function.

In the rabbit, removal of the dorsal root ganglion or section of the ventral ramus of C.1 results in degeneration of from 1 per cent. to 5 per cent. of the myelinated fibres in the most peripheral portion of the hypoglossal nerve (Yee, Harrison and Corbin). Since the monkey rarely has a first cervical dorsal root ganglion (Hartman and Strauss, 1933 ; Corbin,

Lhamon and Petit), the second cervical dorsal root ganglion evidently supplies muscle sense fibres to the tongue muscles of the monkey. However, it is difficult to explain our inability to demonstrate such a contribution in the cat (Hinsey and Corbin, 1934; Corbin and Harrison, 1938). Carleton's work on man, in which there was a loss of sense of position in the tongue following anæsthetization of the lingual mucosa, indicates that intramuscular postural sense in the tongue is very meagre, and might be entirely accounted for in the monkey and rabbit by the small number of fibres from the upper cervical dorsal root ganglia which course peripherally with the hypoglossal nerve.

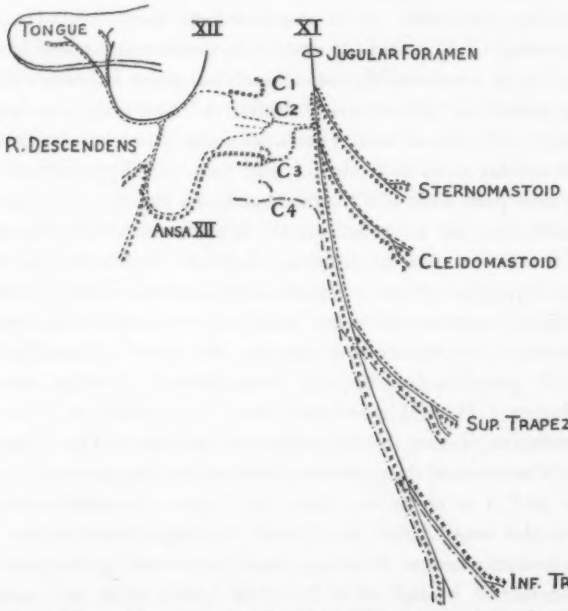

Diagram representing the sensory contribution of the upper cervical spinal nerves to the spinal accessory and hypoglossal nerves in the monkey (*Macacus rhesus*).

Summary and Conclusions.

Degeneration and oscillographic studies were made on fourteen Macacus rhesus monkeys in order to determine the course of proprioceptive fibres from the accessory musculature.

Stimulation experiments indicate that the anastomotic branches between the upper cervical ventral rami and the accessory nerve carry

sensory fibres only. The ventral ramus of C.2 supplies postural sensibility primarily to the sternocleidomastoid muscles and to a lesser extent to the trapezii. The ventral ramus of C.3 also supplies the sternocleidomastoid muscles and contributes a considerable number to both trapezii. The ventral ramus of C.4, however, contributes sensory fibres to the trapezius group only.

As a result of these experiments and previous work on the cat and rabbit we conclude that the accessory musculature (sternomastoid, cleidomastoid and trapezii) is supplied with proprioceptive fibres, the cells of origin of which are situated in the dorsal root ganglia. These fibres pass peripherally over the respective cervical ventral rami finally anastomosing with the accessory nerve before entering the accessory muscles. It seems reasonable to conclude that a similar condition obtains in man.

Section of the ventral ramus of C.2 uniformly resulted in the degeneration of from 2 per cent. to 5 per cent. of the medium-small sized myelinated fibres in the most peripheral portion of the hypoglossal nerve. Since similar degeneration has been obtained following removal of dorsal root ganglion of C.2 in the monkey and of C.1 in the rabbit, we conclude that the degenerating fibres are sensory and proprioceptive to the tongue musculature.

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THE IDENTITY OF MYOTONIA CONGENITA (THOMSEN'S DISEASE), DYSTROPHIA MYOTONICA (MYOTONIA ATROPHICA) AND PARAMYOTONIA.

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SUMMARY.

(1) Introduction.
(2) The distribution of myotonia in myotonia congenita and dystrophia myotonica
(3) Pseudohypertrophy.
(4) Muscular atrophy.
(5) Weakness of muscles and abolished or diminished tendon reflexes.
(6) Autonomic Nervous System.
(7) Cataract.
(8) Mental Symptoms.
(9) Metabolism.
(10) Histopathology.
(11) Electrical Examination.
(12) Familial Incidence.
(13) Age of Onset and Age when Examined.
(14) Course.
(15) Heredity.
(16) Paramyotonia.
(17) Other Conditions in which Myotonia occurs.
(18) Conclusion.
Appendix.

(1) Introduction.

In 1874 Leyden reported a case presenting myotonic symptoms, but interest in and study of myotonia congenita dates from the publication of Thomsen's paper in 1876.

It is possible that Leyden's case was one of dystrophia myotonica, since according to Guttmann (1891) his speech was slow ("langsam und unbeholfen"), a familiar feature of this malady.

Following the appearance of Erb's monograph on Thomsen's Disease (1886), in which the electrical reactions characteristic of myotonia were

first described, cases combining muscular atrophy and myotonia began to be recorded, as for example by Jolly (1896), Hoffmann (1900), and Pelz (1907).

Rossolimo (1902) first suggested that cases presenting both myotonia and muscular atrophy should be regarded as a special variant of Thomsen's Disease.

Batten and Gibb (1909) reported a series of such cases and maintained that they were distinct from Thomsen's Disease, but Steinert (1909) believed that cases presenting atrophy started as typical cases of Thomsen's disease and did not belong to a separate category.

Since this date views have varied. Thus, Adie and Greenfield (1923), Curschmann (1906, 1912, 1915, 1925, 1936), Hauptmann (1916, 1919), Hirschfeld (1911), Nissen (1923), Curtius (1935), and Nevin (1938) have all regarded the two affections as distinct. On the other hand, their identity has been maintained by Noguès and Sirol (1899), Higier (1916), Rosett (1922), Guillain, Bertrand and Rouquès (1932), Massion and Vermiory V. (1936), O. Maas (1933) and Kramer and Quadfasel (1933). The question as to whether myotonia congenita, dystrophia myotonica and paramyotonia are to be regarded as a single, or as distinct, diseases is not a purely academic one, nor one of simple terminology.

If they represent no more than different stages of a single process then the hereditary factors must be the same in each case: that is, both pathology and heredity must be identical.

Clinically it is recognized that in the case of a malady believed to show heritable qualities, there may be clinical variations from family to family affected, yet we do not on this account believe that distinct diseases are in question. In myopathy, for example, the affected members of a single family may all show deviations of the same order from type, as in the topography of the wasting, the presence or absence of pseudohypertrophy and the rate of progress of the disease. Again in Huntington's chorea, age incidence and the relative predominance of chorea and of dementia may vary from family to family (Davenport and Muncey, 1916).

On the other hand, clinical similarity does not necessarily imply complete identity, since factors of heredity may vary.

Thus, there are recessive and dominant modes of inheritance in Friedreich's ataxy, and in the latter case the disease appears later and runs a more benign course. Bell, J. (1935) has shown that maladies with clinical resemblances may have different inheritance factors. In short, it appears that the various types of hereditary ataxy are inherited according to different Mendelian laws.

(2) The Distribution of Myotonia in Myotonia Congenita and in Dystrophia Myotonica.

It has been maintained that while in myotonia congenita (Thomsen's disease) myotonia may be present in most of the striated musculature; in dystrophia myotonica it is essentially restricted to the tongue and thenar muscles.

In our experience, however, the myotonia in the latter disease may be present in almost every muscle of face, trunk and limbs. This conclusion was reached by Adie and Greenfield who say "while it is true that active myotonia is most obvious both to the patient and to the superficial observer in the hand grasps, we feel sure that a careful consideration of all the symptoms and the application of appropriate tests will disclose the fact that it is of much wider distribution in a large proportion of cases."

It is known that in dystrophia myotonica the myotonia disappears in the later stages of the illness in markedly wasted muscles, but the examination of a series of cases in an affected family, where the disease may be observed at different stages of development, shows that myotonia differs in degree and incidence in the different subjects.

(3) Pseudohypertrophy.

Pseudohypertrophy has been observed both in myotonia congenita and in dystrophia myotonica. We have ourselves seen it in trunk and limb muscles in many cases. Case 1 in the Appendix is an example. We have also in a case of dystrophia myotonica seen the combination of muscular wasting with hypertrophy of thenar and hypothenar muscles. Probably the comparatively rare observation of pseudohypertrophy in dystrophia myotonica is due to its early appearance and to its disappearance before wasting occurs.

(4) Muscular Atrophy.

In the differentiation of dystrophia myotonica from Thomsen's disease, the presence of muscular wasting in the former has been regarded as of diagnostic importance (Steinert, 1909, Curschmann, 1906, Hauptmann, 1916), the facial muscles, sternomastoids, supinators and small hand muscles being characteristically affected in this way. Adie and Greenfield (1923), with whose observations our own agree, concluded that there was no characteristic topography of wasting. We have noted wasting in almost all the striated muscles, and also sparing of the sternomastoids, supinators and hand muscles.

Dr. Riddoch, in a private communication, has given us notes of a case

in which he found normal sternomastoids, weakness and wasting of the flexors of wrist and fingers, of supinators, wrist extensors and facial muscles, with myotonia of hands and of orbicularis palpebrarum.

Although in the very numerous cases we have observed we have seen none without some sign of muscular wasting we consider it possible that such may occur. Again, weakness may be observed in certain muscles without unequivocal wasting, and in these the diagnosis of dystrophia myotonica is confirmed by the associated presence of such signs as diminished sexual power, baldness, lack of facial expression, early loss of teeth, or incipient cataract or mental abnormality.

Cases (1, 2, 3, 4) illustrating these points are briefly resuméd in the Appendix.

(5) Weakness of Muscles and Abolition or Diminution of Tendon-Jerks.

Although in his original paper Thomsen referred to neither of these abnormalities, Erb (1886) recorded them in his monograph on Thomsen's disease. Writing in Bumke's Handbuch (1936), Curschmann refers to the diminished frequency with which Thomsen's disease is now diagnosed and cites Sanders' paper (1935) in this connection. It seems that the reason for this is that more exhaustive clinical examination now reveals the signs that we have come to associate with dystrophia myotonica in cases of the kind in which they were formerly missed. A family recorded by Sanders as showing Thomsen's disease is of importance in this connection. It had been earlier recorded by van der Stok (1893) and by Delprat (1892). The last named noticed a defect of speech which is described as "sehr wenig accentuiert": a feature commonly noted in early cases of dystrophia myotonica. Sanders' own description of this family is incomplete, though he mentions the remarkable muscular weakness presented by some of its members.

Hirschfeld (1925) observed in the niece of a typical case of dystrophia myotonica evidences of myotonia only, but ten years later Curtius (1935) saw her and observed abolition of the ankle jerks and diagnosed her as having early dystrophia myotonica. Erb (1889) quoted Uibeleisen (1887) as having noted diminished tendon jerks in a case of Thomsen's disease.

(6) Autonomic Nervous System.

Autonomic imbalance is frequently in evidence in dystrophia myotonica. Case 2 in the Appendix showed myotonia, minimal signs of wasting and weakness, but marked hyperhydrosis. In his first case of

Thomsen's disease Erb reported a marble-like appearance of the skin, and Nissen (1923) found unilateral sweating in a typical case of Thomsen's disease (his own brother). No differentiation between the two maladies is possible, therefore, on this ground.

(7) Cataract.

As is well known cataract is a frequent sign in dystrophia myotonica, but slit-lamp examination was unknown when Thomsen reported his cases, and Sanders does not report that he used this method of examination. Knaur's (1936) cases of supposed Thomsen's disease without wasting showed cataract in two instances. We have examined several cases of dystrophia myotonica in which an ophthalmologist failed to find cataract.

(8) Mental Symptoms.

These are very common in both diseases. Many members of Thomsen's own family were affected, some of them seriously, while in the family examined by Sanders several members with no myotonic symptoms were mentally disordered. In neither family was any detailed psychiatric examination made, but if this had been done, no doubt the neurotic and psychotic symptoms would have corresponded to those described by us (1937) in members of families affected by dystrophia myotonica. There is, in fact, no evidence that the mental symptoms are different in the two diseases.

(9) Metabolism.

Poucher and Woodward (1936) and Nevin (1938) have found differences in metabolism in the two diseases. In Thomsen's disease no creatine was found in the urine, there was increased tolerance for creatine, and the creatinine content of the urine was a high normal. Nevin suggested that this occurred because muscular hypertrophy caused a greater ability to store creatine and to convert it into creatinine, the natural end-product of muscle metabolism.

In dystrophia myotonica metabolism was the same as in cases of myopathy, namely decreased excretion of creatinine, while there was an excretion of creatine.

These observations, however, do not really point to any essential difference between Thomsen's disease and dystrophia myotonica. It is quite feasible that a muscle not affected by wasting, like a normal muscle, may have a normal creatinine metabolism, whereas the pathological metabolism in which creatine is excreted is naturally observed only when there is considerable wasting of muscle.

(10) Histopathology.

Slauck (1936) maintained that the histological pictures of dystrophia myotonica and myopathy were identical. It is obvious then that muscles affected by gross wasting in dystrophia myotonica differ entirely from muscles in a case of Thomsen's disease. No one, as far as we know, has detected any difference between the muscles in Thomsen's disease and those muscles in dystrophia myotonica which show no wasting or weakness.

(11) Electrical Examination.

Eichler and von Hattingberg (1938) have described differences in the behaviour of an active current in the two diseases. We do not doubt that such a difference was found, but this difference was presumably only the difference one would expect to find in a wasted muscle compared to one which was not wasted. These observations, therefore, have no value in distinguishing the two diseases as separate entities.

(12) Familial Incidence.

As already mentioned, Davenport has described different variants of Huntington's chorea, so that in one family mental symptoms predominate, while in others the principal symptoms are those of chorea.

The same principle probably applies in the case of dystrophia myotonica. In some families the myotonic signs tend to predominate, yet these families are not entirely free from other symptoms of dystrophia myotonica.

Some authors have maintained that no case of the one disease occurred in families in which the other was found. We are convinced, however, that this is not so. Boeters (1935) was also of this opinion.

As already pointed out, one member of Thomsen's own family undoubtedly was affected by dystrophia myotonica. We do not know if, in addition to the case examined by Schultze and Steinert, other members of this family were affected by muscle wasting. One of his own sons is described by Thomsen himself in a letter published by Seeligmüller (1879) in the following words, "This son had a slender and feeble physique ('gracilen und schmächtigen Körperbau'), but nevertheless a quite remarkable development of muscle, the like of which I have never seen, which is especially noticeable on the thighs."

Vewey and Legras (1933) reported a family, some of whose members suffered from dystrophia myotonica while others were affected by typical symptoms of Erb's myopathy.

These findings were similar to those obtained by us in one family, of

which many members suffered from typical dystrophia myotonica, but in two boys, both idiots, neither Dr. R. G. Gordon nor one of us (A.S.P.) could find any trace of myotonia. The sterno-mastoids were particularly wasted.

A superficial examination of some of the family Jo (see No. 5 in Appendix) might have led to the belief that certain members were suffering from Thomsen's disease, and if reliance had been placed upon what the original patient had said, it might have been considered that a number of individuals had escaped altogether. Detailed examination, however, showed that practically all had definite signs of dystrophia myotonica. In other families as well, when a patient was found to have typical signs of dystrophia myotonica, we discovered that so-called healthy relatives, who were at work, were affected by definite signs of myotonia, while signs of wasting were very slight.

Isolated cases of dystrophia myotonica in a family have been described until quite recently. Such accounts are, we believe, of no value unless parents, brothers, sisters, children and cousins are examined by experts. We have examined numerous patients who reported that they had no relatives affected like them. When, however, we examined these relatives we found definite signs in them. Numerous individuals with definite signs of dystrophia myotonica maintained that they were perfectly healthy. We have, therefore, to take with reserve reports of isolated cases (we may add that, of course, the diagnosis of myotonia acquisita (Talma-Krabbe) has to be considered in such cases).

(13) Age of Onset and Age When Examined.

As its name implies, myotonia congenita has been supposed to be a congenital affection, while most authorities have described dystrophia myotonica as beginning between the ages of 30 and 40 years.

Examination of the literature, however, as well as our own observations, fails to substantiate any real difference in this respect.

Of the cases of myotonia congenita described by Erb in his monograph, the first two were affected in early infancy, while in the third case the first signs were found at the age of 16 years.

Erb describes in his monograph (1886) three cases who when examined were 14, 15 and 21 years, and he collected numerous cases published by other authors up to 1885. Nearly all these cases were in the early 'twenties when published.

This also holds for the cases published by van der Stok (1893).

In his later article Erb mentioned the age of patients suffering from

Thomsen's disease whose cases had been published by other authors as follows:—

Danillo	24 years
T. Buzzard	16 and 20 „
Uibeleisen	20 „
Jacoby	24 „
Banham	18 „
Blumenau	30 „
Nearonow	23 „
Wising	19 „
Martius and Hansemann	21 „
Renner	17 and 23 „

Some cases which Erb has observed since his monograph was published, were aged 19, 26, 26, 31 and 34 years.

Among these cases some were affected by signs of dystrophia myotonica, as Curschmann has stated (1936).

In many cases in the literature of Thomsen's disease, the age of onset has not been reported.

The belief that the two conditions are distinct rests, therefore, apparently on the fact that myotonica congenita has often been diagnosed in patients who were young, and that those cases have not been followed up.

Again, on the other hand, dystrophia myotonica has sometimes been observed by us as occurring in early infancy. This was pointed out by one of us (O.M.) (1937, pp. 508 and 509) and many cases of dystrophia myotonica reported in this paper showed their first symptoms at any early age.

(14) Course.

There has been a limited number of cases of myotonia congenita, which, on being examined again after an interval of some years have shown definite signs of dystrophia myotonica. Such cases are of great importance in supporting the view that the two conditions are in fact identical. Case 1, for instance (see Appendix), was published by Ironside in 1926 as a case of Thomsen's disease. Although at the present time wasting is not so striking a feature as the myotonia, yet it is sufficient to put the diagnosis beyond doubt, especially as other symptoms (hyperhidrosis and diminished sexual power) are taken into consideration.

Hitzenberger (1920) published a case in which the disease started at the age of 23, and was six years later diagnosed as Thomsen's disease. Nevertheless at the age of 38, the man showed indisputable symptoms of dystrophia myotonica.

A case of Steinert (1910) was a typical case of Thomsen's disease for many years, but atrophy of the testicles ensued at the age of 45.

Kolb, Harvey and Whitehill (1938) reported the following case: A boy began to suffer from myotonic symptoms at the age of 8 years. He was demonstrated by another author as a case of Thomsen's disease when aged 14. It would appear that nothing suggesting dystrophia myotonica was detected at the time. Kolb and his co-workers examined him at the age of 33. They found myotonia only in his thenars, with no hypertrophy or atrophy of muscles, but early baldness and high palate. A slit-lamp examination could not be made.

The diagnosis was dystrophia myotonica sine atrophia.

Curschmann (1936) maintained that there was a marked difference between the two diseases, as dystrophia myotonica was always characterized by cachexia at a later stage (p. 441), while myotonia congenita took one of three courses: it remained at a standstill, was remittent or was slowly progressive (pp. 446 and 464).

We have, however, examined numerous cases with definite symptoms of dystrophia myotonica, some over 50 and up to 70 years of age, who were in no degree cachectic.

On the other hand certain cases of Thomsen's disease in the literature show a general progressive physical deterioration.

The grandfather of Dr. Thomsen himself, who in his youth was a page at the Danish Court, a post that presupposes a reasonably good physique, had later to give up a military career because of his state of decrepitude.

(15) Heredity.

Thomsen, Nissen and Sanders have described how myotonia congenita has occurred in subsequent generations of a family. One of us (O.M.) has shown, as other authors had previously, that the same holds for dystrophia myotonica (1937, p. 514). It would be out of place here to discuss the form which the heredity takes. It is enough to point out that there is no difference between the two disorders with regard to the mode of transmission.

(16) Paramyotonia.

Cases published by Eulenburg (1886) as well as by Martius and Hansemann (1889) in which myotonia occurred only in cold weather, were given the name of "paramyotonia," and regarded by various writers as constituting a different entity from myotonia congenita. Curschmann (1936, p. 462) discussed these cases and maintained their close relationship to, if not identity with, myotonia congenita, on the ground that such cases were

found in families affected by Thomsen's disease. Nevertheless later on in the same article (p. 484) he stated that it was probable that this rare condition paramyotonia congenita was an independent disease (Selbständige Krankheit).

The fact that most cases in which myotonic symptoms occur are more markedly affected in cold weather and freer from inconvenience in warm weather makes it probable that so-called "paramyotonia" is only a slight variant.

In this connection the following case is of interest, which we examined some years ago.

E. M., a male, aged 35. A cousin was described by O. Maas and H. Zondek (1920) as a typical case of dystrophia myotonica. E. M. worked as a farmer. Thyroid a little enlarged. He had a haggard look. Face was thin, blowing out cheeks was weak, sterno-mastoids as well as all the muscles in the right upper limb and in both lower limbs were normal, but all the muscles in the left forearm as well as the left thenar muscles were wasted. Myotonia was not observed in any muscle on examination, but he reported typical myotonic stiffness in his hands in cold and wet weather.

This case shows that the symptom "paramyotonia" may occur in families affected by dystrophia myotonica.

Similar cases have been reported by Schott (1935). They suffered from intermittent myotonic symptoms and wasting in the small muscles of the hands. Schott named the malady "Paramyotonia congenita."

(17) Other Conditions in Which Myotonia May Occur.

There are two groups of cases which may give rise to the wrong diagnosis of myotonia congenita.

Cases have been described by Hoffmann and by Kramer (1918) in which the symptoms of myotonia evidently resulted from thyroid malfunction. Other cases of this type have recently been reported by Nevin (1938).

A typical case was observed at the National Hospital in 1934.

S. McL., a female, aged 20 (Case of Dr. Martin). There was myotonia, and some muscles appeared hypertrophied. After treatment with thyroid extract, myotonia and hypertrophy disappeared.

The other group of cases in which myotonic symptoms occur have been described by Talma (1892) and has recently been discussed fully by Krabbe (1934). In these cases myotonia, and also muscle hypertrophy, came on after an infectious disease, probably always in combination with polyneuritis. A case which we considered as belonging to this group was an in-patient at the National Hospital under the late Dr. Adie in 1926.

W. W., a male, aged 62. He had complained two years previously of pins and needles which later developed into stiffness. On examination typical myotonia was observed in all the limbs. There was no wasting. Alterations in his lenses were found, but these were different from the type which occur in dystrophia myotonica (see Adie and Ironside, 1925).

In our view the acute onset of myotonia, as well as the age at which the disturbance started, are strongly against the diagnosis of "myotonia congenita." We agree with Krabbe's opinion that such cases are true "myotonia acquisita," *which is in no respect related to "Thomsen's disease."*

On the other hand, however, not all cases published as coming under this diagnosis do in fact belong to the type described by Krabbe. A case demonstrated by Jolly, for instance (1896) is undoubtedly one of dystrophia myotonica, for a son of that patient has been described by one of us (Bielschowsky, Maas, Ostertag, 1933) as a typical case of that disease. Also one of Talma's cases is very doubtful as no infectious disease preceded the myotonia.

Myotonia was further described by Schlesinger (1902) as a rare symptom in cases of syringomyelia. We think it likely that those cases were similar to the case published by Maas and Critchley (1934-35) in which dystrophia myotonica was combined with syringomyelia.

Lastly, we would mention an interesting observation made by Worster-Drought (1932) who described a family affected by an obscure hereditary nervous disease. One member was affected by myotonia of upper and lower limbs in addition to other organic signs in the central nervous system. It would appear improbable that this was a case of dystrophia myotonica.

We cannot, therefore, deny that the symptom of myotonia may occur in a familial disease of the nervous system other than dystrophia myotonica.

(18) Conclusion.

We have traced the conception of the syndrome myotonia congenita or Thomsen's disease in the literature. We have examined in detail those characteristics in virtue of which some writers have sought to distinguish it from dystrophia myotonica. All the evidence goes to show that so-called myotonia congenita is merely an early stage of dystrophia myotonica. Nearly all the cases of myotonia congenita described in the literature have been between the ages of 17 and 30. Almost no case has been watched over a number of years. In certain cases where this has been done, signs of dystrophia myotonica have been found to develop. In recent years, as remarked by Curschmann, myotonia congenita has been very rarely

diagnosed. This is evidently because neurologists are on the look-out in a case of myotonia for slight wasting, for cataract as revealed by slit-lamp examination, for atrophy of the testicles and other symptoms both in the patient himself and in the members of his family. Where these occur myotonia congenita is not diagnosed. Yet a generation ago, when these symptoms were not looked for, myotonia congenita was more frequently diagnosed.

We have attempted to show that none of the arguments are really valid which have led to the separation of the two diseases myotonia congenita and dystrophia myotonica. These are based on the alleged difference of distribution of the myotonia and the wasting throughout the body; the presence of pseudo-hypertrophy, absence of certain reflexes, mental symptoms and the rest.

The only sense in which myotonia congenita can be said to exist is that in certain families there is a tendency for the myotonia to be prominent and for the wasting and other symptoms to be less pronounced and to come on at a later date. Nevertheless such families are more truly said to exhibit a variant of dystrophia myotonica than a separate disease.

Similarly, if a patient is found to be suffering from paramyotonia, that is myotonia which may occur in cold weather, we suggest that a complete examination of his relatives will reveal some members who show symptoms of dystrophia myotonica. The symptom-complex described by Talma and Krabbe as "Acquired Myotonia" is, however, quite a different disease from dystrophia myotonica, which is a hereditary condition.

We hope, therefore, that we have proved beyond reasonable doubt that myotonia congenita, dystrophia myotonica and paramyotonia are essentially one and the same disease. We consider that it would be logical to widen the conception of Thomsen's disease to cover all the symptoms included under the other two names. The two latter names might be abandoned, thus allowing *the whole disorder to be known as Thomsen's disease or myotonia congenita.*

In conclusion we would express our thanks to the members of the honorary staff of the National Hospital and of other hospitals for their assistance in providing material and also to Mr. C. Goulden and Mr. T. C. Summers of the London Hospital for the examination of numerous cases with regard to cataract, and to Dr. L. D. Bailey for the electrical examination of our cases.

We are both also indebted to the Medical Research Council for grants in connection with this work.

APPENDIX.

Case 1.

J. C. G., aged 34 (case of Dr. Brinton). Complained of stiffness in all his limbs and in moving his eyes, since infancy. When questioned he said that his face had definitely become thinner during the last two or three years. On examination, there was hypertrophy of some of the muscles of the upper and lower limbs, especially the deltoids, biceps brachii, muscles of the forearms, quadriceps and muscles of the calves. There was slight, but definite wasting of the temporal and facial muscles, sterno-mastoids, peroneal muscles. There was slight weakness of his buccinators and also in his grip. There was slight but definite weakness in dorsal flexion of the feet and of the toes. The left triceps jerk was absent or only showed a flicker. There was typical myotonia in the tongue, thenars, hypothenars, extensors and flexors of the forearms. There was also some hyperhidrosis and diminished sexual power. His memory had deteriorated in the last three years and his general interest in life had waned.

Case 2.

X. Y., a male, aged 26. His father aged 61, healthy, able to do very hard physical work, but suffered from stiffness in his arms for some decades. The description of the stiffness was quite typical, and he became bald at an early age. He was not examined by us.

X. Y., an only child, feels perfectly healthy, is exceptionally intelligent and is engaged in scientific work. The stiffness in the arms and legs has been present for many years, he thinks since infancy. He did not, however, pay much attention to this. He complained of double vision and squint if he moved his eyes quickly. He sweats readily and tires more quickly than most people, e.g. when swimming. His hair receded from his forehead as early as the age of 14 years. On examination mechanical myotonia was seen in his tongue in quite a marked degree. The strength of the buccinators was slightly diminished. There was a slight myotonic response on tapping the thenars, hypothenars, flexors and extensors of the forearms. Dorsal flexion of the left foot was not very strong. Slight myotonic facies.

He said that many members of his family had suffered from very early loss of their teeth and also from early baldness. All the children of one of his father's sisters had lost all their teeth before the age of 21. The youngest sister of his father had died at the age of 12. She was mentally disordered. The youngest daughter of another sister of his father went to a special school for mental defectives. Several of his cousins suffered from cramps.

Case 3.—(A case of Dr. D. Brinton).

A. Bo., aged 31, complained of general weakness since infancy. He was operated on for cataract at the age of 31. General stiffness in slight degree since infancy.

Slight wasting of facial muscles.

Definite wasting of sterno-mastoids.

Forearms poor, but no special wasting of supinators, hand muscles not wasted.

Weakness of facial muscles, both grips, dorsal flexion of the feet.

Mechanical myotonia in thenars, hypothenars, extensors and flexors of the forearms.

The other members of his family examined were his father, his father's sister, his own brother and three sisters. All these showed signs of dystrophia myotonica.

Case 4.—(A case of Dr. S. K. Westmann).

Mrs. G., aged 30. The brief report on her family gave no reason for supposing that other members of her family were affected by myotonia. Mrs. G. had suffered from intermittent stiffness in her upper and lower limbs for ten years. This stiffness would disappear for weeks and at times for months, but became more evident after she became pregnant in February, 1938.

On examination, slight but typical myotonia was found in many muscles of upper and lower limbs. It was much more conspicuous at the second examination carried out 14 days after the first one (in June, 1938).

A doubtful wasting was found in her temporals. Although right handed, her right fore-arm was a little smaller than the left. The right supinator longus was a little smaller and weaker than the left, as confirmed by Dr. Riddoch. She reported also that she sometimes suffered from fingers which would go quite white and dead.

No other abnormality was found.

Case 5.—(A case of Dr. A. W. Spence).

J. J. A female, aged 44. She was healthy till the age of 38, when she showed marked signs of dystrophia myotonica, although the supinators are still good! One maternal aunt had cataract.

Five sisters and two brothers of this woman were examined as well as nine siblings in the next generation, all of whom were affected with more or less marked signs of dystrophia myotonica, and yet none were incapacitated.

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CLINICAL INVESTIGATION OF OLFACTORY FUNCTION IN BRAIN TUMOUR PATIENTS.

BY JOHN D. SPILLANE.[1]

RECENT electro-physiological studies on the sense of smell in animals (Hasama, 1934, Adrian and Ludwig, 1938) have prompted the publication of this paper, which deals with the application of the new methods of quantitative olfactometry, as devised by Elsberg and his associates (1935), in clinical neurology. Elsberg's studies arose out of a desire to improve the early diagnosis of olfactory groove meningiomas and progressed to an investigation of alterations of olfactory function in tumours arising in the substance of the cerebral hemispheres. A large number of cerebral tumours have now been investigated (Elsberg, Levy and Brewer, 1935 and 1936) and a summary of their findings has recently been published (Elsberg and Stewart, 1938).

The claims are striking and have been the subject of much comment in American neurological circles. Up till the present time, however (October, 1938), there have been no similar studies reported by other workers, except those of Adler and Finley (1938) who recorded their results in a series of brain tumours.

There is thus no need for an apology for this paper, which is based on an independent study of the method in 140 individuals, normal and diseased, carried out at Cardiff and in Dr. Elsberg's laboratories at the Neurological Institute of New York.

THE PRINCIPLE OF THE TESTS.

An odour cannot be appreciated if the breath is held. Before it can be appreciated and identified a sufficient quantity of that odour must impinge upon the olfactory membrane with a certain degree of force. There must, therefore, exist a level of threshold stimulation at which the odour is first detected. Now, as pointed out by Elsberg, all previous tests of olfactory function have entailed sniffing of odorous substances by the individual being tested, so that accurate quantitative measurements have been impossible. It is difficult to measure the degree and force of sniffing.

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The new tests were devised to exclude this variable factor ; a known volume of odour was *injected* into the nostrils *during a period of voluntary apnœa,* so that the level of threshold recognition could be ascertained.

The Apparatus and Procedure.

A full description of the technique will not be furnished here, only the essentials will be enumerated. The apparatus consists of a standard test bottle, with inlet and outlet tubes, containing a known volume of odorous substance (coffee or citral), a glass syringe and a set of nose-pieces. Two tests are made ; the blast injection test and the stream injection test.

The blast injection test.—A known volume of air is injected into the test bottle and released into one nostril, through the nose-piece attached to the outlet tube, during a period of voluntary apnœa. The number of c.c. of odour that must be released into one nostril in order that the odour be identified is termed the minimum identifiable odour (M.I.O.). Be it noted, that the volume of odour released from the test bottle must necessarily equal the volume of air previously injected into the test bottle from the syringe.

The stream injection test.—This procedure is used for the study of olfactory fatigue. A stream of air, of known volume-rate, is passed from a tank of compressed air through the test bottle and thence to the nostril, for a period of thirty seconds. The patient is instructed to breath quietly through the mouth. Blast injections of the previously determined M.I.O. are then made at thirty-second intervals and the time that elapses before the odour is again identified, is measured. This is the duration of olfactory fatigue.

The two tests are performed in both nostrils and with the two substances, coffee and citral. Thus, the M.I.O. and the duration of olfactory fatigue are determined for coffee and citral in each nostril. The procedure, although relatively simple of execution, with practice, requires considerable attention to detail if results are to be reliable. The whole test can be completed in about one hour if the patient is co-operative. Frequently, however, it is advisable that the patient be subjected to testing with only one substance at the first interview.

The Results.

We shall first consider the normal findings and then proceed to a discussion of those obtained in cerebral tumour patients.

A study of forty normal individuals led Elsberg to assert that the M.I.O. for coffee and citral were 8—10 c.c. and 6—8 c.c. respectively, while the

duration of olfactory fatigue varied between 1·5 and 2·5 minutes for coffee, and 2·5 and 3·5 minutes for citral. Adler and Finley (1938) reported that they frequently observed the M.I.O. to be lower than the above figures, namely, 3 to 4 c.c. for coffee and citral, but that in no instance was it higher than Elsberg's figures. They do not mention the number of their controls.

In the present series of 140 observations there were 60 normal controls, mostly medical students. Although the majority, 41, or 66 per cent., were discovered to have M.I.O.s confirming Elsberg's figures, it became amply evident that there were plenty of individuals whose olfactory acuity was of a lower level. The findings of Adler and Finley were also corroborated.

TABLE I.

Minimum identifiable odour (M.I.O.) in 60 normal controls.

M.I.O.	Number	
	Coffee	Citral
1— 3 c.c.	0	6
3— 6 „	10	4
6—10 „	41	41
10—15 „	9	7
15—20 „	0	2
20—30 „	0	0

In this control group, needless to say, care was taken to exclude local nasal conditions that would lessen olfactory acuity. All individuals were first subjected to a Zwaardemaker test.

Olfactory fatigue studies were made on only thirty of the above control group, but even in this small series marked variations were found and it was concluded that the duration of normal olfactory fatigue in this test ranged from ½ to 4½ minutes. Here again, the majority, 23, or 80 per cent., gave figures in accordance with Elsberg's findings. (Table II.)

TABLE II.

Olfactory fatigue in thirty normal controls

Olfactory Fatigue	Number	
	Coffee	Citral
½—1 min.	1	0
1—2 min.	3	4
2—3 min.	24	22
3—4 min.	2	2
4—5 min.	0	2

Results in Brain Tumours.

Elsberg's observations have led him to conclude that pressure on one olfactory nerve, as by olfactory groove meningiomas, suprasellar meningiomas, pituitary tumours that have extended beyond the confines of the

sella turcica and aneurysms of the internal carotid artery, leads to a raised M.I.O. on that side. If both olfactory nerves are pressed upon, the M.I.O. of both sides is higher than normal, the greatest increase being found on the side most affected.

In supratentorial intracerebral neoplasms and in large dural growths buried in the brain, the M.I.O. is not raised but the duration of fatigue is prolonged on the same side as that of the neoplasm.

In frontal lobe tumours that extend to the undersurface of one lobe so that the olfactory bulb or tracts are subjected to direct pressure, the M.I.O. on the affected side is larger than normal *and* the duration of olfactory fatigue is prolonged.

Elsberg also added that many degenerative and inflammatory conditions of the brain could provide similar olfactory patterns.

In this investigation 80 consecutive suspect brain tumour patients were studied. At the outset, it should be realized that Elsberg has repeatedly stressed the fact that the value of the tests lies not so much in diagnosis as in localization of brain tumours. However, as precisely similar olfactory patterns may be obtained in other organic brain diseases, it should be remembered that in the interpretation of results, the dice will be heavily loaded in his favour if the observer merely publishes those cases in which a brain tumour was subsequently found to exist. And surely, if the diagnosis of tumour has already been made and localization decided, before olfactory tests are made, then there is little practical value in the method whether the tests succeed or fail in localization. The only criterion of the actual value of the tests would be the percentage successful localizations in previously diagnosed, but unlocalized, brain tumours. It is this point which has been continually ignored in all published reports.

In the latest report (Elsberg and Stewart, 1938) the claim is made for 74 per cent. correct localization in 101 supratentorial tumours ; no localization in 22·9 per cent. and incorrect localization in 2·9 per cent. In 81 per cent. of 150 patients who eventually proved to have no tumour, the olfactory tests gave no evidence of a localized lesion. Such claims, if confirmed, would confer on quantitative olfactometry a degree of exactness and usefulness in clinical neurology, which would compare very favourably with that obtained in ventriculography and encephalography. A hitherto neglected cranial nerve would, in the future, deserve the same attention of the clinician that he now devotes to the optic fundus exclusively. That such will not be the case seems indicated from the results of this study.

In Table III are outlined the values of the M.I.O. and the duration of olfactory fatigue in 35 brain tumours. In only 11 instances was localization

effected by the olfactory tests; in two additional cases the tumour was lateralized to the correct hemisphere, but to the wrong lobe. Localization was incorrect in 7 instances, while no information was obtained in the remaining 15 cases. In the latter group, however, were two internal carotid artery aneurysms, one cerebellar tumour and four pituitary tumours which had not extended beyond the sella turcica.

Of three subfrontal meningiomas two were localized; no information was obtained in the third.

Of eleven frontal tumours four were correctly localized; localization was incorrect in two while in the remaining five cases no information was obtained.

Among seven pituitary tumours there were two in which reduction of olfactory acuity suggested that the tumour had extended beyond the sella turcica. This was confirmed in both cases by operation. In one of them, Case 3, marked progression of the lesion, under X-ray therapy, with rapid reduction in visual fields was found to be accompanied by corresponding elevation of the minimum identifiable odour for both nostrils.

The above 35 cases were the proven brain tumour patients in a series of 80 consecutive brain tumour suspects. In the remaining 45 individuals, epileptics, psychotics, arteriosclerotics, etc., no instance of an olfactory pattern was encountered which pointed to a local brain lesion. In many, however, there was considerable diminution of function of the olfactory brain. As a control group they also served to indicate that there exist wider values for the M.I.O. and the duration of olfactory fatigue than those laid down by Elsberg.

Discussion.

In attempting to account for the discrepancy between the above findings and those of Elsberg a few theoretical considerations might prove helpful and instructive. Phylogenetically old, the rhinencephalon in man can play but little part in establishing contacts with his environments and marked variation in reaction to olfactory stimuli would naturally be expected in different individuals. In relatively few is the olfactory sense highly developed; in a correspondingly large group minor differences would hence be of little significance.

Histological studies of recent years (Cajal, 1911 and Winkler, 1918) have indicated the existence of connections between the two sides of the rhinencephalon. Olfactory nerve fibres crossing in the anterior commissure have been repeatedly demonstrated. Hence, it might be expected that unilateral olfactory disturbances might be compensated by activity of the opposite side. That such does actually happen is suggested by

Elsberg's demonstration that overstimulation of one olfactory membrane can result in reduction of contralateral olfactory acuity. The recent observation of the author (Spillane, 1938) that a condition of "olfactory alloæsthesia" may arise in unilateral cerebral disease, strengthens this point of view. Under this title was described a condition found in unilateral cerebral tumours characterized by a tendency for a stimulus applied to the olfactory membrane on the tumour side to be appreciated as if it arose from the opposite side. Such indications of bilaterality of function and innervation would render the interpretation of unilateral disorders of olfactory function extremely hazardous. But, as Elsberg has remarked, while commenting on the conclusion of Henschen (1919) in a clinical-pathological study (that the olfactory centres are so completely innervated bilaterally that unilateral alteration of olfactory function rarely arises in unilateral disease), former tests of olfactory function have been too gross to detect finer disturbances.

A second approach in this study is gained from a consideration of the physiological processes involved in the recognition of an odour. With gradually increasing olfactory stimuli several stages in the recognition of an odour can be detected. The first sensation experienced is one of odour-perception, a threshold level. With increase in the strength of the stimulus comes the realization that the odour is familiar, but recognition is still lacking. Finally, the stimulus reaches a strength at which the odour is named (the minimum identifiable odour, M.I.O., of Elsberg). Now, in comparing the olfactory acuity of a group of individuals it must be realized that wide variations *in these three stages* exist, so that a true index of olfactory acuity may not be obtained if thresholds of *odour-recognition* are investigated. The threshold of *odour-perception* may be the same in many individuals, but varying ability in the naming of the odour concerned would lead to great differences in the thresholds of *odour-recognition* in those subjects. Similarly, individuals who name odours at a certain level of stimulation may actually possess vastly different abilities in odour perception. Hence, in studying the olfactory functions in any group of subjects, a truer index of comparison would be the thresholds for odour-perception rather than those of odour-recognition. The latter is not a true threshold stimulus as it involves previous experience and other mental factors.

From the practical standpoint the tests present several drawbacks. The most outstanding is that their success is too dependent on the co-operation of the patient. In trained individuals, such as formed the control material on which were based several of Elsberg's observations, the tests

are relatively simple. In any large group of hospital patients, however, many will be encountered who prove utterly incapable of grasping the essentials of the manœuvres and on whom the tests cannot be completed. Moreover, from the very nature of their lesions many brain tumour suspects, are quite unable to offer the necessary degree of co-operation. In the present series, there were approximately a further twenty subjects with brain tumours on whom the tests could not be carried out. Adler and Finley experienced similar results.

In the determination of the duration of olfactory fatigue—that part of the procedure which proved to be of the least practical value—a fallacy becomes apparent which theoretically may be of some account. It is this. When the M.I.O. is first determined the identity of the odour is *unknown* to the subject. When the fatigue tests are made, however, the odour is *known* to the patient. Now, one has repeatedly demonstrated the fact that M.I.O.s before and after the identity of the odour is revealed are often entirely different. Before, the value may be 10 c.c., and afterwards, much less, 6 or 7 c.c. Elsberg himself has demonstrated that a reduction in the value of the M.I.O. can be obtained if the blast injection is made at a moment when the subject recalls that odour to his memory. Hence, the values obtained for the duration of olfactory fatigue cannot be regarded as a *quantitative* index of the refractory state of the olfactory apparatus at the time of examination.

Summary and Conclusions.

A study has been made of Elsberg's recently introduced method of quantitative olfactometry. 140 individuals were investigated; 60 normal controls, and 80 suspect brain tumour patients.

It was concluded that the new tests of olfactory function far excel those of former years in both accuracy and reliability. In addition, they are quantitative in nature, being based not upon the principle of sniffing of odorous substances, but upon that of the injection of known volumes of odour into the nostrils during periods of voluntary apnœa. By this method a study can be made of the threshold levels of odour-perception and odour-recognition (minimum identifiable odour or M.I.O.) for any odorous substance. A measure of the duration of the relative refractory period of the olfactory apparatus may also be obtained by studying the recovery-rate in odour-recognition following prolonged overstimulation of the olfactory membranes (duration of olfactory fatigue).

Values for the M.I.O. and duration of the olfactory fatigue in 60 normal individuals indicated that there is a wider range of variation than

that indicated by Elsberg. Nevertheless, it was confirmed that the majority of individuals possess roughly similar degrees of olfactory acuity when gross local conditions of the nasal passages have been excluded.

TABLE III.—DATA IN THIRTY-FIVE CASES OF BRAIN TUMOUR.

	Minimum identifiable odour				Olfactory fatigue					
	Coffee		Citral		Coffee		Citral			
Case	Right	Left	Right	Left	Right	Left	Right	Left	Location	Confirmed diagnosis
1	13	22	30	30	10	10	—	—	Midline	Pineal tumour
2	9	10	4	5	5½	1	1	1	—	Suprasellar meningioma
3	7	7	7	7	4½	3	2	4½		Pituitary
	11	11	8	11	9	6	8	10	Midline	extrasellar
4	8	30	8	20	10	10	4	6½	Left	Left hemisphere
5	13	7	7	5	4½	½	1½	1½	—	Right internal carotid artery aneurysm
6	30	8	30	15	—	10	—	5½	Bilateral	Meningioma at base
7	18	8	16	4	10	10	7	2	Right frontal	Cerebellar
8	6	30	13	30	10	—	6½	—	Bilateral	Left temporal
	9	30	22	27	10	—	2	7½	frontal	
9	6	7	3	4	1	3	4½	3½	—	Pituitary
10	25	30	15	30	4½	—	½	—	Subfrontal	Subfrontal meningioma
11	20	30	20	30	1½	—	10	—	Subfrontal	Subfrontal meningioma
12	4	4	4	6	1½	4½	1	1½	—	Right internal
	5	5	5	4	0	0	0	2½	—	carotid artery aneurysm
13	8	30	5	9	2	—	1	10	Left frontal	Left occipital
14	8	7	8	7	3½	10	1	3½	—	
	11	14	10	16	1	4	7	2½	? frontal	Right frontal
15	7	9	7	7	10	3½	7½	3	Right frontal	Pituitary extrasellar
16	4	5	4	5	0	1½	1½	2	—	Right frontal
17	12	8	11	7	½	0	0	½	Right	Right
	11	8	9	7	2	½	1½	1	extracerebral	intracerebral
18	19	5	13	5	2	2½	1½	0	Right subfrontal	Left frontal
19	5	8	5	8	1	1	6½	1½	—	
	10	7	8	5	4½	2	5	2½	Right frontal	Left frontal
20	6	8	4	6	2	3½	2½	0	—	Right frontal
21	6	7	8	8	2½	2½	1	4½	—	Left
	7	6	5	5	0	2½	7	1½	—	frontoparietal
22	8	9	3	6	2	2	1½	0	—	Left frontal
23	11	10	6	5	2	6	1	1	—	Right cerebellar
24	5	7	4	4	0	0	2½	1½	—	
	2	5	2	4	3½	2	1	8½	—	Pituitary
25	5	10	6	5	3	3½	1	3	—	Pituitary
26	30	30	18	30	—	—	1½	—	Subfrontal	Frontal meningioma
27	18	30	10	17	5	—	0	0	Subfrontal	Suprasellar glioma
28	25	15	23	13	3½	0	10	10	Right frontal midline	Right frontal
29	30	12	30	9	—	0	—	1½	Midline	Pituitary
30	12	9	9	8	2½	2	0	1	—	Pituitary
31	11	8	18	6	3½	0	6½	2	Right frontal	Right frontal
32	22	8	10	7	2½	3½	1½	5	? Right subfrontal	Left cerebellar
33	18	30	29	30	7	3½	3½	—	Subfrontal	Left temporal
34	7	8	4	4	1½	3½	½	2½	—	Subfrontal mainly left
35	6	10	3	7	½	½	½	3½	—	Right temporal

By this procedure further knowledge of olfactory functions may be gained. For instance, that olfactory fatigue is central rather than peripheral in origin, is suggested by the observation that the duration of

olfactory fatigue is frequently prolonged in cerebral tumour patients on the side of the lesion.

The classification of odours may be studied by this method (Elsberg, 1935).

The practical application of the tests in clinical neurology is, however, limited, thus far, to the early detection of interference with the function of olfactory nerves and bulbs. Pressure by tumours, such as olfactory groove meningiomas, sphenoid ridge meningiomas and other neoplasms in the subfrontal region, lead to a raising of the M.I.O. on the side of the lesion. Such tumour pressure may thus be detected before complete anosmia has resulted, so that complete removal of the tumour may be attempted before it has attained large proportions.

Evidence is adduced that the tests may be of some value in indicating the spread of a pituitary neoplasm beyond the confines of the sella turcica. In such cases, raised M.I.O.s are evidence of pressure by the tumour upon extracerebral olfactory pathways. Intrasellar pituitary growths do not interfere with olfactory function.

Confirmation is lacking that the tests are of value in the localization of intracerebral growths. Of 11 frontal tumours only four were correctly localized by the presence of prolonged duration of olfactory fatigue, without change in the M.I.O., on the side of the tumour.

Finally, the high degree of sustained co-operation that is required of the patient further limits the practical application of the method in clinical neurology.

I wish to thank Dr. C. A. Elsberg for giving me the opportunity to make this investigation at the Neurological Institute of New York.

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Notices of Recent Publications.

Histological Technique for Intracranial Tumours. By Dorothy S. Russell. Oxford University Press. 1939. Pp. 71, with 6 illustrations. Price 7s. 6d.

It has long been recognized that more is needed for the histological diagnosis of intracranial tumours than paraffin sections stained with hæmatoxylin and eosin. But in spite of the increasing interest in intracranial tumours there are still too few laboratories, at least in this country, where any but the most routine staining methods are employed. Dr. Russell's little book should, therefore, be of great value. She does not pretend to include in it all the methods that have been or may be applied to the study of intracranial tumours. For that a more comprehensive text book such as the Microtomist's Vade-Mecum is needed. Rather she gives a full and practical description of the methods which she has found to be most useful. The book must, therefore, be judged by what it includes rather than from its omissions, and as a practical guide to well-tried methods of staining it deserves nothing but praise. The most obvious omission is that of the Gros Bielschowsky technique. This method has proved so valuable in correcting current theories as to the relationship of nerve fibres to the different forms of neurofibroma that it might well have been included. The wisdom of including the smear technique for rapid diagnosis of the various forms of glioma may be doubted since it is only of value to those who have already had considerable experience of the gliomas and the book seems to be written for the tyro rather than the expert.

The six plates contain beautiful illustrations of the results which may be obtained by the various staining methods and should be of great value both as a guide and as an incentive to careful technique.

The Surgery of Pain. By René Leriche. Translated by A. Young. London: Baillière, Tindall and Cox. 1939. Pp. 512. Price 21s.

The reader of Professor Leriche's book will gladly admit the truth of its translator's prefatory remark that it betrays "freshness and originality of outlook," but as he studies its pages he may also feel that these qualities are most fruitful when applied to the logical interpretation of a carefully ascertained body of fact.

In other circumstances freshness and originality are too apt to lead their possessor into the wilderness of arid speculation.

Professor Leriche would be the last to deprecate criticism since he is himself a bold challenger of accepted views and their presentation, saying that modern surgical literature is often mortally dull and sometimes unreadable because of its reiterations and contradictions. No one could say that his own book is dull, though it is not free from the last-named defects.

Words are apt to have a magic quality and in these pages the word "sympathetic," both as adjective and as substantive is magical indeed in its power to provide—often with little further amplification—explanations of the causation of pain, and reasons for the failure of this and that surgical method of pain relief.

A characteristic example of the way in which the sympathetic is incriminated as a cause of pain is seen in the chapter dealing with the extremely rare condition that he calls "post-traumatic spreading neuralgia." The syndome so named has hitherto found description in French neurological literature under the title of "ascending neuritis" or "reflex paralysis" (Babinski), and an account of it may be found in this Journal (1919, **42**, 349). It appears typically to result from a very minor injury to an extremity, in particular to a digit, such as a prick, a cut or even an injury not involving a breach of the skin. The clinical picture, which is painted in stronger colours by Leriche than by previous observers, includes pain of growing intensity and extent, spreading from the site of the injury proximally up the limb. The affected hand becomes moist, red and cold, the skin and nails atrophy and finally the entire limb may be severely wasted. Even more serious are the associated mental changes, for "in a very few days the patient's mental balance becomes changed" and even if we succeed in curing the pain "the brain never again becomes normal."

Leriche suggests that such a peripheral injury to a region rich in nerve endings is followed by an immediate vasomotor disorder which passing through a phase of vaso-constriction ends in passive vasodilatation. Although it is the nerve endings of the spinal nerve that are damaged, the reaction is of the sympathetic, nor is this reaction purely local for he adds that "a disordered condition of the mind materialises under our eyes, and the mechanism of its production appears to be vascular." Of the steps by which this exceedingly complex and remote reaction is brought about no very clear statement is given, nor is the explanation for the excessive rarity of this disastrous result of peripheral trauma entirely convincing. This rarity, Leriche maintains, is all a matter of individual temperament. Each person reacts in his own fashion and "we don't know why it develops in some people and not in others." It must indeed be an odd physiological mechanism that reacts in this wholly capricious and unpredictable manner.

It is perhaps in connection with the so-called spreading post-traumatic neuralgia that Leriche is least convincing, yet the order of pathological theory displayed in this chapter sets the standard obtaining elsewhere in the book. In the matter of the treatment of this syndrome he is scarcely more enlightening, for to a list of useless surgical procedures on the nervous system succeeds a list of procedures to be undertaken, and to this the general statement that none even of these is successful "because we don't know enough."

It may well be that current physiological doctrines need constant and critical examination, but surely they cannot usefully be replaced by the invoking of "temperament" or by the easy doctrine that "each person reacts in his own fashion." This is the negation of knowledge and no advance can be looked for along this primrose path of facile speculation.

Anatomie Chirurgicale du Crâne et de L'Encéphale. Par CH. CLAVEL et M. LATARJET. Paris: G. Doin. 1938. Pp. 258, figs. 151. Price 200 Fr.

This admirably written and illustrated work has been designed primarily for the neuro-surgeon, and is the fruit of a collaboration between anatomists and surgeons.

The illustrations have been drawn from anatomical specimens specially prepared

for their purpose: namely, to display the topographical relationships between the skull and its contents, and between the various structures, nervous and vascular within the skull. There are also many clear radiograms in some of which post mortem lipiodol injections reveal the ventricular system and the arterial supply of the brain.

The text is clear, methodically arranged and exhaustive, and is excellently supported by the illustrations.

The authors are to be congratulated upon a fine piece of work, well planned and well executed, and one that will be as useful to the neurologist as to the neurosurgeon.

La Syphilis du Système Nerveux. By A. Sezary. Paris: Masson et Cie. 1938. Pp. 287. Price 48 Fr.

This book deals with only certain aspects of the subject from which it takes its title, and is not concerned with the clinical description of the various manifestations of nervous syphilis.

It discusses a number of the problems of neuro-syphilis, which, so far as they have any unity, have to do with the general reaction of the nervous system to the syphilitic infection.

The opening chapter deals with the state of the cerebrospinal fluid from the time of infection onward, and the course of latent syphilitic meningitis. The author then goes on to consider the etiology of nervous syphilis, and he expresses the belief (based on statistics) that adequate treatment of syphilis in its early stages renders the subject more liable to subsequent nervous involvement than no treatment at all. Dealing in the next part of the book with the pathogenesis of nervous syphilis he suggests that the central nervous system does not share in the antibody reaction which takes place in the rest of the body after infection, but that spirochætes which have lodged in it find themselves in an unfavourable medium, and take years to adapt themselves to it sufficiently to enable them to multiply freely.

He admits however that this theory, like all the other theories of the pathogenesis of G.P.I. has its weaknesses.

He is an advocate of the treatment of G.P.I. with pentavalent arsenic and considers that cases which do not respond satisfactorily to such treatment do not respond well to malaria either.

The book has many points of interest and is obviously written by one with wide experience.

Personality Structure in Schizophrenia. A Rorschach Study. By Samuel J. Beck. New York: Nervous and Mental Disease Monographs. 1938. Pp. 88. Price 2 dollars.

The writer of this monograph is prominent among those who have furthered the use of the Rorschach ink-blot method as a diagnostic aid in psychiatry. He is now concerned also to interpret what is characteristic of the schizophrenic response to the test, and thereby to gain more insight into the psychological structure of the personality of schizophrenics. His interpretations, however, depend on inferences, which may or may not be valid, as to the significance

of particular aspects of the response, e.g. a low percentage of "good forms" in a patient's answers is taken to indicate a "feeble prehension of reality. As if from falling hands, the world slips, towards which he grasps." *Ex pede Herculem* can surely be a deceptive mode of thought in these large matters of personality. Although Dr. Beck lays chief stress on this interpretative aspect of the study, more valuable are the actual findings, in a group of 81 paranoid or indeterminate schizophrenics, which he has evaluated statistically, comparing them with a group of 33 normals of about the same age and sex distribution. These useful results are presented more clearly and readably than is usual in Rorschach reports, and are well illustrated by data from individual records.

Uber Gewalttätigkeitsverbrecher und ihre Nachkommen. By KONRAD ERNST. Berlin: Monographien aus dem Gesamtgebiete der Neurologie und Psychiatrie. 1938. Pp. 142. Price RM. 19·70.

This study was undertaken to throw light on the hereditary aspects of criminal behaviour in Germany, so that the question might presently by considered of whether such measures as compulsory sterilization or prohibition of marriage should be applied to criminals, as they have already been in that country to certain supposedly transmissible physical and mental disorders. The investigation cannot be said, however, to disclose anything definite: it supplies interesting social data about men who committed crimes of violence, and their children, but it does not permit any conclusion as to whether the social deficiencies of these children are mainly attributable to their environment or to hereditary factors. Ninety-three criminals, selected from a register, were the starting point of the inquiry; fourteen of them were found to have died. Their 684 wives, children, and stepchildren were investigated, nearly half of them being seen personally. The main outcome of the investigation was to confirm the general belief that the worse the parents, the worse the children, as a rule. Such factors as living in slums, having a delinquent mother, being of poor intelligence and abnormal personality, were also found to have been adverse, as would be expected.

The Postnatal Development of the Human Cerebral Cortex. Volume I. The Cortex of the Newborn. By J. L. CONEL. Cambridge, Mass.: Harvard University Press. 1939. Pp. 106, with 98 plates. Price 35s.

The present is the first volume of a work intended to trace the postnatal development of the cerebral cortex in the human subject, and deals with the cortex of the newly-born infant.

A series of clear and beautifully produced plates show the cortical appearances as seen by the cresyl violet, Cajal and Golgi-Cox methods. The text describes in detail the cell and fibre architectonics of the various cortical regions.

This work will take its place beside the familiar works of Campbell, Brodmann and Economo, and it is no unworthy member of a masterly series

Conel finds that the definitive cytoarchitectonic pattern of the cerebral cortex, as revealed by cresyl violet staining, is already established in the normal full-term infant at birth.

The Morphology of the Brachial Plexus, with a note on the pectoral muscle and its tendon twist. By WILFRED HARRIS. Oxford University Press. 1939. Pp. 110. Figs. 87. Price 25s.

This book embodies the results of an extensive study of the brachial plexus throughout a wide range of the animal kingdom from Amphibia and Reptiles to Primates. In all the plexus was dissected in 158 animals and human subjects. In addition the structure of pectoralis major is studied. It is found in man and some of the apes to consist in three portions, clavicular, manubrial and sterno-costal, the first-named being peculiar to man and three of the anthropoids. The twist in the tendinous insertion of the lowest portion is related to the activity of climbing and is distributed accordingly in the animal kingdom.

The supply of the dorsal aspect of the hand by the median and ulnar nerves also comes under consideration, and the author, as a result of his comparative studies, suggests that the dorsal cutaneous supply on the hand and fingers and of the dorsal interosseous muscles in man is due to latent, essentially dorsal fibres which, instead of passing into the posterior cord, are carried in the ventral cord and given off terminally in the median and ulnar nerves as in certain reptilian plexuses.

The book is illustrated by a large series of diagrams of the brachial plexus. This study, which has been carried out over a number of years, has clearly been a labour of love with Dr. Harris, who is to be congratulated upon bringing it to so fruitful a conclusion.

Hérédité et Epilepsies. Par L. MARCHAND. Paris: Editions de la Nouvelle Revue Critique. 1938. Pp. 123. Price 36 Fr.

In his introduction, the author points out that since in certain States measures spoken of as "eugenic" are taken in respect of "hereditary epilepsy," it becomes of increasing importance to ascertain whether, and to what extent, a heritable form of epilepsy occurs. Reviewing previous statistics, and conclusions drawn therefrom, he points out that vague and conflicting definitions of the term epilepsy vitiate most of the earlier views on this subject. The conception of an idiopathic epilepsy is becoming progressively narrowed with the advance of knowledge in pathology, physiology and biology, and it is now widely realized that epilepsy is often but one of many possible expressions of a variety of pathological changes in the brain. The substitution of the term "the epilepsies" for the old term "epilepsy" expresses this changed point of view.

In the general population the proportion of so-called epileptic subjects is approximately 2 per thousand. From an analysis of all the available information, and after the exclusion of those cases due to external and adventitious factors, he concludes that there is nothing that can be called a familial epilepsy capable of direct transmission without the intervention of external factors. In congenital affections resulting from developmental defects of the ectodermal layer, epilepsy, when it is seen, is no more than a symptom of a cerebral lesion; it is symptomatic and not simply inherited.

Factors that may play a part in a familial epilepsy are syphilis, alcoholism, intoxications and other factors adverse to health, but true heredity is not in question.

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